



A novel and Emerging Coronavirus Infection: Repurposing and Scale of Advances of Therapeutics, Immunotherapeutics and Vaccine Development

Tapas Kumar Mohapatra¹, Reena Rani Nayak², Arijit Mondal³, Sitansu Sekhar Nanda⁴✉

¹Associate professor, HOD, Department of pharmacology, IMT Pharmacy College, Gopalpur, Puri, 752004, India

²Odisha drugs and Chemicals Ltd, Mancheswar Industrial estate, Bhubaneswar, Odisha, India

³Department of pharmaceutical chemistry, Bengal college of pharmaceutical Technology, Dubrajpur 731 123, West Bengal, India

⁴Department of Chemistry, Myongji University, Yongin, 03674, South Korea

E-mail: nandasitansusekhar@gmail.com

✉ **Corresponding author:**

Department of Chemistry, Myongji University, Yongin, 03674,
South Korea

E-mail: nandasitansusekhar@gmail.com

Citation

Tapas Kumar Mohapatra, Reena Rani Nayak, Arijit Mondal, Sitansu Sekhar Nanda. A novel and Emerging Coronavirus Infection: Repurposing and Scale of Advances of Therapeutics, Immunotherapeutics and Vaccine Development. *Drug Discovery*, 2021, 15(35), 06-33

ABSTRACT

A new coronavirus (nCOVID-19) has appeared in China for the first time, inducing various effects in humans and strongly linked to those induced by SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). Several cases of this infection with the coronavirus respiratory syndrome have also been identified in over 215 countries. More than 16,482,747 cases of coronavirus disease 2019 have been recorded since December 2019 and about 653,325 deaths around the world have occurred. In the USA, Brazil, India, Russia, South Africa, Mexico, Peru, Chile, Spain, United Kingdom, Italy, Germany and France, most cases have been registered. This public health epidemic has been the emergence of this emerging illness which threatens to propagate exponentially across the globe. The accepted cases are subdivided into four groups dependent on clinical evidence, which involve mild, moderate, serious and critical instances. Of the active cases, approximately 1% were seriously/critically ill and 99% were in mild conditions. The infection fatality incidence was roughly 6%. This analysis focuses on knowledge currently available about COVID-19's etiology, clinical signs, diagnosis, and mode of action. In addition, according to current evidence, we provide a summary of the



diagnosis methods and treatment for this condition. This review information will help the physician identify and manage COVID-19 effectively.

Keywords: nCOVID-19; Vaccine; Therapeutics

1. INTRODUCTION

Epidemiology

Novel corona virus disease 2019 (COVID-19) a global pandemic began in Wuhan city of china on December 2019.¹ It initiated infection in 2nd January 2020, near about 41 Patients with tiredness, fever, cough and myalgia admitted in the health centre of China. Later every patient associated with severe pneumonia confessing to the intensive care unit (ICU) because of serious respiratory disorder (30%) and 6 of them died.² Within a short duration, these new genetic variants of Beta CoV grow over a wide geographic area. As per WHO, 2020 the rate of COVID-19 infection spread over 200 countries and territories. Worldwide 83,652 people affected and the number of fatalities is over 3,000 on February 28, 2020. Further, the rate of infection increased, around 1,285,257 people affected and fatality rate approximately 5.4% (70,344/1,285,257) on April 6, 2020.³ Initially, Chinese patients (72,314) with suspected, confirmed, and symptom-less conditions revealed various crucial epidemiological aspects of COVID-19. Out of 1,023 mortality cases, most patients were above 60-80 years of age (20.3%). However, children within 0-9 years old reported with few cases. Compared to females, males are more prone to this disease (China 1.06:1, Hubei 1.04:1 and Wuhan 0.99:1, based upon population scales).^{4,5}

Taxonomy, Structure, Genomic Characteristics and CoVs Replication Pathway

Coronaviruses (CoV) are enveloped RNA virus belonging to family Coronaviridae, with variable sizes (80 to 120 nm in diameter).⁶ International Committee for Taxonomy of Viruses (ICTV), a CoV Study group reported about four genera of Coronaviridae that is α , β , γ , and δ coronavirus.⁷ The group/genus α contains HCoV-NL63 and HCoV-229E, CoV of humans. The group/genus β comprised of (A, B, C, and D) lineages that carry HCoV-OC43 and HCoV-HKU1 (lineage A), SARS-CoV (lineage B), and MERSCoV (lineage C). Particularly, HCoV-229E and HCoV-OC43 have acknowledged in 1960, develop common cold symptoms. HCoV-NL63 genomic sequence was isolated from a child with an age of only 6 months and identified. γ and δ coronavirus find out in mammal contain avian coronaviruses not discovered in humans.⁸

5-Methylguanosine cap at the beginning are the constituent of SARS-CoV (SARS-CoV-2) and MERS-CoV genomes, a total of 6-10 genes in between and poly-A tail. It translated by two open reading frames having different overlapping followed by ribosomal frame shifting and converted into two uncoated non-structural polyproteins (nsps).⁹ Glycoproteins formed through the process of glycosylation by Golgi apparatus. At Spike 1 (S1) area of the receptor-binding domains (RBD) SARS-CoVs species use the N-terminus and other species uses C-terminus. Cleavage of S protein by host transmembrane protease, cathepsin, transmembrane serine protease type 2 (TMPRSS2), and angiotensin-converting enzyme 2 (ACE2) receptor, that manages the entry of SARS-CoV (SARS-CoV-2) and HCoV-NL63 viruses. Proteolytic S protein cleavage accompanied by the fusion of plasma membrane or by acidified endosomes to facilitates entry of the viral genome towards the host cell.¹⁰

Viral S protein on interacting with host ACE2 results in downregulation of ACE2a through a negative feedback loop mechanism that controls its angiotensin I substrate towards its enzyme, ACE and increased its activity. Thus, enhanced ACE activity automatically elevates angiotensin II levels that, followed by its receptor binding angiotensin II receptor, type 1 (AGTR1A), increase pulmonary vascular permeability.¹¹ Whereas, cell adhesion molecule-1 (CEACAM-1) and dipeptidyl peptidase 4 (DPP4) receptor responsible for MERS-CoV binding.¹²

Inside the host cell, virion genomic RNA responsible for the movement of the replicase gene, which encodes replicase-transcriptase complex (rep1a and rep1b) with its co-terminal polyproteins (pp1a and pp1ab). CoVs species use smooth sequence (50-UUUAAAC- 30 from the rep1a to rep1b) with a pseudo-knot of RNA for frame-shifting of the ribosome during translation.¹³ Replicase polyproteins in connection with nsps responsible for cleavage of two or three proteases that encoded by CoVs. Encoding of papain-like proteases (PLpro) done inside nsp3 in SARS and MERS, while in other serine protease (Mpro) encoding done inside nsp5.¹⁴ Replicase-transcriptase complex (RTC) formed by the assembled nsps via its RNA-dependent RNA polymerase (RdRp) that builds a controlled status for viral RNA synthesis.¹⁵

Finally, structural proteins with S, E, and M possess a translation of virus and that push into the endoplasmic reticulum (ER) in the cytoplasm.¹⁶ Encapsidation (enclose viral nucleic acid within a capsid) of viral genomes performed by mature virions N, M and E protein and produce the CoV envelopes, respectively. On the other hand, nucleocapsid binds to N and M protein and accelerates

the formation of virus-like particle (VLP) that complete virion construction and the M protein binds to the nucleocapsid and encourage the completion of virion assembly.^{17, 18} Next, The virions move towards the cell surface membrane in the presence of lipid bilayer vesicles and ultimately released by the process of exocytosis. However, in some CoVs the S protein, does not accumulate into virions, transport towards the surface of the cell and conciliates fusion between infectious cells and the adjacent uninfected cells, that leads to the establishment of multinucleated giant cells, not detected or counteract by virus-specific antibodies but permit the virus to outspread inside an infected organism.¹⁸

However, variation in ACE2 expression level and frequency of allele in-between populations is the main consideration. Uniform responsiveness for SARS-CoV-2 among individuals can be another underlying cause for rapid growth over different human populations and continents.

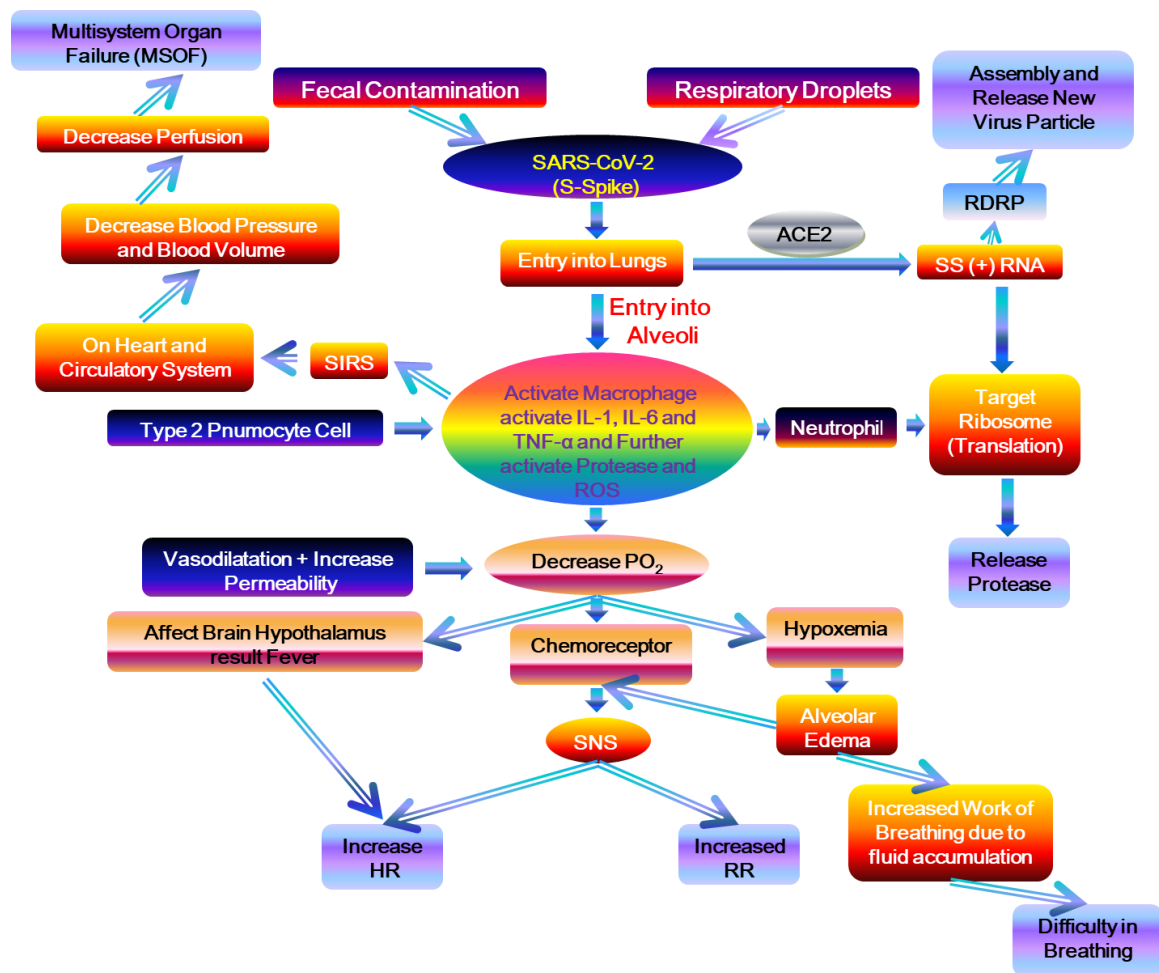


Figure 1: Physiological mechanism of SARS-CoV-2 in schematic illustration.

Pathogenesis of CoVs

Earlier notions indicate that mild and limited infections of the respiratory system in humans only cause by CoVs, however, an upsurge of SARS and MERS CoVs alter this notion.¹⁹ CoVs cause lower respiratory tract infection and HCoV-NL63 is responsible for intense laryngotracheitis (croup) in humans, whereas HCoV-229E is obvious for mice infection.²⁰ nCoV-19 and HCoV-OC43 have logical genetic variation while HCoV-OC43 can infect mice and several herbivorous species. It has been reported that multiple sclerosis (MS) develop by CoVs of humans. An elderly person with cardiovascular disease, hypertension, diabetes, chronic bronchitis, chronic obstructive pulmonary disease, cerebral infarction, Parkinson's disease, and cancer mainly affected by nCoV-19.²¹⁻²³

The peoples in this era have felt the appearance and infestation of 3 formerly unidentified coronaviruses. SARS-CoV is responsible for the development of SARS (severe acute respiratory syndrome) was identified in 2003, flares up in the Guangdong territory of China. HCoV-EMC (human coronavirus EMC) first found out in an old man in Bisha with 60 years of age, belong to Saudi Arabia (KSA), and another in Doha, Qatar passed away due to community gained pneumonia and failure of kidney on 23rd of September 2012, communicated by the World Health Organization (WHO).²⁴ Since then, several tragedies have been communicated

in Europe and the Middle East, and later renamed by International Committee on Taxonomy of Viruses (ICTV) as Middle East respiratory syndrome coronavirus (MERS-CoV).

Bamboo bats, MERS-CoV reservoir, discovered in Hong Kong in 2007, phylogenetically resemblance to other C lineage betacoronaviruses, Japanese and *Pipistrellus Tylonycteris* bat (Pi-BatCoVHKU5 and Ty-BatCoV-HKU4).^{25,26} MERS-CoV genomic analysis showed its genome size constitute of 30, with 106 bases having S and RdRp genes. There are also 90% amino acid sequence with Ty-BatCoV-HKU4 and 70% amino acid sequence that resemble with Pi- BatCoV-HKU5.^{27, 28} RdRp analysis manifested, MERS-CoV is a forefather of nCoV (novel coronavirus) with lineage C betacoronaviruses declared in December 2019 and officially named SARS-CoV-2.²⁸ Till now, several animals hypothesized as the reservoir for SARS and MERS CoVs, but still now animal sources are not confirmed. It has been reported that 'wet markets' placed in South China with living wild animals is the beginning place for breakouts COVID- 19. However, snakes as a viable source for nCoV- 19 are under disputed condition. Some animals like canine, equine, porcine, bovine, and camel also conspicuous in Betacoronaviruses. Horseshoe bats are considered as a prime reservoir for this nCoV, and the mid hosts responsible for the transmission of the virus to human are dromedary camel and palm civet for MERS-CoV and SARS-CoV, respectively. Also, it has reported that, other wild animals or via pangolin (*Manis javanica*) nCoV- 19 may communicate to humans, expectedly link to the wet market of Wuhan.²⁹ It is suggested that the SARS epidemic scenario similar to the arrival of COVID 19 as an interspecific transmission, from bats to other animals and then ultimately to humans.

Generally, SARS-CoVs infect the lungs epithelium and also penetrate into dendritic cells and macrophages of humans. Infected cells of SARS-CoV-2 liberate interferon gamma-induced protein 10 (IP10), macrophage inflammatory protein (MIP) 1 α , monocyte chemoattractant protein 1 (MCP1), granulocyte-colony-stimulating factor (GCSF), tumor necrosis factor- α (TNF α) and interleukins (IL2, IL7, IL10), like several proinflammatory cytokines and mediator for inflammatory and immune suppressive diseases.³⁰⁻³²

However, conveyance of SARS-CoV-2 from human-to-human occurs through direct contact with infected individuals, mainly in the group and in-between family members, signifies spread of pathogen before the beginning of symptoms. SARS-CoV and SARS-CoV-2 average contagious period of 1.1 to 1.2 h with half-lives were alike in aerosols.³³ As a reflection of SARS-CoV, air-borne, and fecal-oral communication, the chance of SARS-CoV-2 may not be lay down.

Human to Human contagious infection spread worldwide announced as Pandemic disease. Close to other RNA viruses, this family of virus specified with remarkable genetic variation and the top rate of recombination empower them to be comfortably disseminated between humans and animals globally. Thus, many CoVs without producing life-threatening diseases exist inside human and animal society. Sometimes, recombination of the viral gene inside random transitional hosts starts infectious strains which are tremendously morbidic for the human being.³⁴ SARS-CoV-2 possesses a unique characteristic that quickly grows around the world. The under way CoV warning that came out in China quickly proliferate to other countries and WHO already announce it as a world health disaster or pandemic.

General Clinical characteristics of CoV and COVID-19

CoV may contaminate humans and animals and develop certain complications of the respiratory system and gastroenteritis.^{35, 36} Lakhs of human death occurs because of nCoV-19 has already identified in between January-august 2020.

Travel histories to the endemic location with close contact records are important parameters for patients identification.³⁷ Fever (83–95%), shortness of breath (19–53%), cough (59–80%), and muscle ache (11–42%), is the standard sign of COVID-19 as like as SARS and MERS. However, several patients experience headache, confusion, rhinorrhea and sore throat just before the beginning of a fever.²³ Some cases having coughing up of blood (hemoptysis) and recently a large proportion of patients found relatively asymptomatic.^{22, 35} Usual or lower white blood cell counts (leucopenia), lower platelet count (thrombocytopenia), including the elevated C-reactive protein level provoke symptom of rheumatoid arthritis may experience by patients with COVID-19.^{2, 22} In few patients, dyspnoea appears within 5–13 days following the onset of illness, while in others, it may be absent.³⁵ Inadequacy of breath and ischemic hypoxia in sick patients can rapidly advance into severe respiratory distress syndrome (17–29%), acute infectious septicemia and dysfunction of different organs in 8 days following manifestation.^{22,38} Angiotensin-converting enzyme 2 (ACE2) a principal receptor of SARS-CoV-2 exhibited in the gastrointestinal epithelial cells of human beings, while gastrointestinal shedding of virus and transmission through fecal-oral route is sensible. However, negative was reported for nasopharyngeal tests, but positive results for the rectal swabs.^{36, 39} Stool specimen of infected patients detected with live virus strongly narrates stool transmissible effect even after the discharge of patients for a prolonged time. Thus, rectal swabs examination is criteria fix for patient discharge can be regarded as a caution for COVID-19 nosocomial and community outspread. Nevertheless, hyposmia and hypogeusia are a sign and primary alarm during rapid self-isolation.⁴⁰

Radiological Features of COVID-19

Prior detection and treatment of COVID-19, chest computed tomography (CT) scan, and chest X-ray are the efficient radiological examinations.⁴¹ The radiological findings of COVID-19 pneumonia imitate the feature of influenza and pneumonia associated with SARS-CoV, and MERS-CoV.⁴²⁻⁴⁶ The radiological finding of Wuhan shows that, bilateral pneumonia (75%) expressed by some patients, and remaining (25%) infected patients expressed with unilateral pneumonia. CT scan patients showed increased attenuation in the lung with preserved bronchial and vascular markings in 14% patient.² A subsequent study, reported that mainly peripheral abnormality (54%) and they observed right lower lobes infection of affected segments (27%) among 849 patients.⁴¹ The radiological evaluations of COVID-19 pneumonia on chest CT are fluctuating and comprehensive. Serious COVID-19 cases include many ground-glass opacity (GGO) or hazy opacity lesions with interlobular/intralobular septal thickening, bilateral patchy shadowing, and abnormalities of the interstitium are the common finding of chest CT found in a range of (4-82 %) patient. Rarely reported findings are pulmonary cavity lesion, excess fluid accumulation in the pleural cavity (pleural effusion), and lymphadenopathy.⁴⁷⁻⁵⁰ Sometime, RT-PCR shown positive results with no alteration in CT for SARS-CoV-2. However, symptomless patients manifesting positive CT detection doubtlessly create challenges towards patients with false-negative RT-PCR outcome.⁵¹

Diagnostics

Some diagnostic measures for COVID-19 recommends by Centers of Disease Control and Prevention. Specimens/swab mainly collect from upper and lower (oropharyngeal or nasopharyngeal and bronchoalveolar lavage or endotracheal tube) respiratory tract and often specimen collect from the nasal wash, or during aspiration. During pneumonia, RT-PCR examination of the specimens and the often serological tests may also be preferred. Recently, within 3.5-4 hr results are given commercially, obtained from Roche (cobas® SARS-CoV-2) test system which approved by the USFDA. It is an assay for dual-target occupied with fully processed (negative, positive and internal) control to certify accuracy and selectivity (SARS-CoV-2 RNA and E gene fragment are constant in all members of the Sarbecovirus subspecies). On FDA approved another qualitative test system from Cepheid Inc (USA) (Xpert® or Xpress SARS-CoV-2), and it takes 45 minutes to give the result declared on March 21, 2020. Positive results detected on the basis of the presence of over one targeted gene. The present methods of screening believe in the existence of the plentiful genome of viruses at the sample collection site. Several reports showed that top level of IgM antibodies expressed in subclinical and symptomatic patients, following 5 days beginning of the disease. It suggests that ELISA based IgM assay in combination with PCR amplify the sensitivity detection.⁵²

Table No. 1. Complication, Laboratory and Radiological feature of COVID-19

System	Symptom	X ray of Chest
Respiratory	<ul style="list-style-type: none"> Sore throat Cough Strongness of breath Rhinorrhea 	<ul style="list-style-type: none"> Patch showing Multiple GGOS Septal thickening Interstitial abnormalities
Gastrointestinal	<ul style="list-style-type: none"> Hypogeusia Hyposmia Nausea 	Blood test <ul style="list-style-type: none"> Increase C reactive protein Decrease WBC count Decrease lymphocytes Decrease platelet
CNS and Others	<ul style="list-style-type: none"> Fever Fatigue Headache Myalgia Confusion 	Diagnostic <ul style="list-style-type: none"> RT-PCR IgM ELISA

2. REPURPOSING AND DEVELOPMENT OPPORTUNITIES OF DRUGS AGAINST COVID 19

Pharmacological management

Many countries provide the greatest efforts to execute control master plan and development of proper preventive/proper precautionary measurement. Now existing antiviral drugs or directly acting antiviral drugs and vaccines are not available for the human and animal treatment in CoV induced pneumonia or infections (COVID-19).⁵³⁻⁵⁵ Regrettably, the latest CoV proliferating with contrasting sequence of RNA creates challenge towards drugs and vaccine development against different variants of CoV. Thus

repurposing of antiviral and anti-inflammatory drugs both synthetic and natural source is essential for the management of COVID-19. Several on-going trials are now designed based on repurposing. Likely, several trials were started off to test and develop the specific or promising drug or vaccines candidates and antibodies specifically targeting SARS-CoV-2. Based upon on their target site present therapy may be broadly classified into two groups.

1. Directly acting CoV inhibitors or Viral genomic replication inhibitor - (I) Viral enzyme inhibitors or nsp inhibitors such as inhibitors of 3-chymotrypsin-like protease, inhibitors of RNA-dependent RNA polymerase (RdRp), inhibitors of papain-like protease (II) viral entry inhibitors (towards human cells)
2. Human immune system modulators- (I) Innate response booster; (II) Inflammatory processes (that cause lung injury) inhibitor.

Available therapeutics for management of COVID-19 are mainly based upon earlier experience in the management of SARS CoV and MERS CoV which was done preclinically or clinically. The extensive drugs therapies that can be efficacious in COVID-19 management are remdesivir, lopinavir/ritonavir combination along with interferon- β , convalescent plasma, and monoclonal antibodies (mAbs). However, clinical efficacy, and safety studies, should take into consideration prior to their use in pneumonia patients of COVID-19.

3. REPURPOSING BASED PRECLINICAL AND CLINICAL TRAILS

Viral Protease inhibitor

Ivermectin

FDA approved Ivermectin as an anti-parasitic agent. It also showed its activities against human immunodeficiency virus (HIV) and dengue virus. Viral nuclear protein transportation is crucial for reproduction and development. However, inhibition of nuclear transportation is a workable approach in therapy toward RNA viruses. Ivermectins inhibit (up to 5,000-fold) SARS-CoV-2 RNA after 48 h of infection has already proven in in-vivo study. Ivermectin's anti-parasitic use has already proved its safety profile. Following to prove its efficacy now Peter Doherty Institute of Infection and Immunity and Melbourne and Monash BDI, Clayton, Victoria start its trials to solve the adequate dosing on the management of COVID-19.⁵⁶⁻⁵⁹

Lopinavir/Ritonavir

During replication, cleavage of precursor polypeptides and encoding of aspartyl protease enzyme playing an important part by HIV pol gene. Thus lopinavir and ritonavir combinably inhibit protease of HIV. Lopinavir and ritonavir individually showed their capacity to inhibit the CoV or 3-chymotrypsin-like pro protease (3CL1 protease) and too efficacious against SARS and MERS proved in several *in-vivo* and *in-vitro* investigation.⁶⁰⁻⁶³ Lopinavir/ritonavir combination also expressed little benefit in mild to moderate COVID-19 patients (NCT04252885) observed during the clinical trial.⁶⁴ Clinically Lopinavir/Ritonavir application is a time restricting step because they are mainly effective during the early phase of viral replication (initial 7-10 days) but delayed therapy initiation had no effect, move it backward.^{63, 65} Clinically lopinavir 400 mg and ritonavir 100 mg combination used a dose of 500 mg twice daily for 14 days used in COVID-19 treatment.^{66,67} In another trial, no benefits of lopinavir and ritonavir combination were observed on severe COVID-19 patients (ChiCTR2000029308).^{67,68} However, side effects may be worse by combination therapy in patients of COVID-19.

Camostat mesylate

SARSCoV-2 or virus-induced mast cell activation release multiple pro-inflammatory leukotrienes, cytokines (cytokine storm) and chemokines lead to the development of inflammation (bronchoconstriction). Mast cells also contain the serine protease tryptase ACE2, which convert angiotensin I to angiotensin II via an active renin angiotensin system. Thus, Camostat mesylate, an approved agent to treat pancreatitis in Japan and South Korea, prevents entry of nCoV cell in-vitro through inhibition of the host serine protease, (TMPRSS2). This new mode of action provides a supplementary drug target for future research developed mutually by the University of Aarhus, Denmark and German Primate Center-Leibniz Institute for Primate Research, Gottingen and plans for the Phase I/II CamoCO-19 trial (NCT04321096). Cocystal and Kansas State University Research Foundation mutually develop novel protease inhibitor to treat CoVs. Recently they start its preclinical testing.⁶⁹

RdRp inhibitor

Remdesivir

Remdesivir or GS-5734 is a monophosphate prodrug, after metabolism converted to an active C-adenosine nucleoside triphosphate (structure resemblance to adenosine) and shows a wide range of antiviral activities in case of RNA viruses. In developing viral RNA, it enter and obstruct the action of RdRp and reduce developmental stage of the viral RNA chain and replication of viral genome. Gilead Sciences (USA) originally developed it against the Ebola virus, and for its low EC₅₀/safety and selectivity towards host

polymerase, it showed promising result in National Institute of Allergy and Infectious Diseases and PALM Clinical Trials of Congo, Beni (NCT03719586) during the recent Ebola outbreak.⁷⁰ However, *in-vitro* results of remdesivir exhibit antiviral activities against SARS-CoV (SARS-CoV-2) with EC₅₀ 0.77 μ M and EC₉₀ of 1.76 μ M, respectively, and in murine lung infection models with MERS-CoV, it prevented lung hemorrhage.⁷¹⁻⁷³ Single and multiple dose intravenous infusion showed linear pharmacokinetics with a long half-life of greater than 35 h in between 3-225 mg and well tolerated with no proof of liver or kidney toxicity in phase I clinical trials. However, administrations of multiple-dose, increase reversible aspartate aminotransferase and alanine transaminase. The latest loading dose under study is a single 200-mg, followed by a daily infusion of 100 mg. Previously it was reported that on the 7th day of hospitalization remdesivir was applied on first COVID-19 patient in the USA and its condition improved on the 8th day with no noticeable adverse effect.⁷⁴ Multiple trials and phase III randomized control trials (RCT) are conducted in different countries including china (NCT04292899, NCT04292730, NCT04280705 and NCT04252664, NCT04257656), expected to be over in May 2020.⁶⁸ Primarily, remdesivir is not FDA-approved drug but recently Japan ratifies application of remdesivir on COVID-19 patient.

Favipiravir

Favipiravir (T-705), is a prodrug of a purine nucleotide (favipiravir ribofuranosyl-5'-triphosphate), its structure resembles with endogenous guanine, flu drug originally started by Fujifilm Toyama Chemical, Japan under the brand name Avigan. Fujifilm has started phase III trial of this drug and also enhanced its manufacturing. It is an approved drug for influenza treatment. Through competitive inhibition it inhibits RNA-dependent RNA polymerase and halt viral replication.⁷⁵ *In-vitro* study (Vero E6 cells) revealed its low EC₅₀ (61.88 μ M/L) against SARS CoV-2.⁷² Previously, randomized, multicenter trial of favipiravir was conducted and differences in clinical recovery at day 7 were observed as compared to Arbidol/Umifenovir (n = 120) to treat moderate (71.4 % favipiravir and 55.9 % Arbidol, P = .019) and severe (No significant differences were observed) COVID-19 infections.⁷⁶ Recently Glenmark Pharmaceuticals received approval from India's drug regulator (DCGI) on antiviral tablet Favipiravir in late April and has commenced Phase-III trials in India. Another Indian manufacturer, Strides pharma so far go ahead sending the favipiravir to gulf region territories.

Ribavirin

Ribavirin, an analog of guanine, inhibits viral RNA-dependent RNA polymerase. Combination therapy and high concentrations (1.2-2.4 g orally every 8 h) required to inhibit viral replication, at this higher dose Ribavirin produce hematologic (hemolytic anemia in than over 60 % of patients) and liver toxicity (elevated transaminase in 75% of patients) limits its use.⁷⁷ Clinically Ribavirin in combination with lopinavir/ritonavir and interferons- β 1b (NCT0427668 in Hongkong) and again Ribavirin in combination with interferon- α 1b (ChiCTR2000029387 in China) showed no noticeable effect but toxicity was appeared (requir blood transfusions in 40% of patients) in the treatment of MERS.⁷⁸ Primarily, Ribavirin is a teratogen and contraindicated in pregnancy. The inconclusive efficacy data with ribavirin for other nCoVs and its toxicity narrate that it has limited merit for treatment of COVID-19.⁷⁹

Virus-Cell Membrane Fusion Inhibitor

Hydroxychloroquine and Chloroquine

Hydroxychloroquine and Chloroquine are well-known for treatment of malaria and systemic lupus erythematosus (SLE) and rheumatoid arthritis like persistent inflammatory diseases (RA). Hydroxychloroquine and Chloroquine inhibit fusion, a process of cell membrane because of which virus entry into the host cells, required glycosylation of ACE2 cellular receptor, rising neutralizing pH of endosome.⁸⁰ These agents also have a capacity for reduction of cytokine production and inhibition of autophagy and lysosomal activity in host cells, act as immunomodulatory agent.^{81,82} Hydroxychloroquine and chloroquine with EC₅₀ 6.14 and 23.90 μ M in *in-vitro* showed inhibition of SARS-CoV-2, 24 h after the incubation.⁸³ Recent information from china revealed that chloroquine was successfully used to treat over 100 COVID-19 cases due to increased viral clearance, decreased disease progression and improved radiological findings.⁸⁴ Likely, many randomized trials speedily conducted in China, specify productivity of hydroxychloroquine for COVID-19-associated pneumonia. However, validations of these claims are needed in near future. Similarly, A recent open-label nonrandomized clinical trial from France (n = 36, 20 in the hydroxychloroquine group and 16 in the control group) revealed that hydroxychloroquine (200 mg, by mouth every 8 hours) improved virologic clearance (Day 6, nasopharyngeal swabs in hydroxychloroquine = 70% (14/20) vs nasopharyngeal swabs in control 12.5% (2/16), P = .001). Similarly, azithromycin and hydroxychloroquine combination was trialed against hydroxychloroquine monotherapy showed superior viral clearance (Combination = 6/6, 100% vs hydroxychloroquine alone = 8/14, 57%).⁸⁵ Small sample size (n=20 and only 6 receiving hydroxychloroquine and azithromycin), additive cardiotoxicity with combination therapy do not approve this regimen without additional studies. Another randomized trial was conducted in China (n=30, for 5 days) showed the effect of hydroxychloroquine

with standard care (supportive care, interferon, and other antivirals) and hydroxychloroquine alone on viral clearance (on day 7, 86.7% vs 93.3%, $P > .05$) respectively.⁸⁶ However, a physiologically based pharmacokinetic modeling (PBPK) study suggested best dosing regimen for hydroxychloroquine and chloroquine in COVID-19 treatment start with an oral dose of 500 mg (once or twice daily) and then it progressively reduce to 400 mg for 1 day accompanied by 200 mg (twice daily) respectively. Further studies are needed to delineate the optimal dose for COVID-19.⁸⁴

Latest clinical study from France manifest Hydroxychloroquine and azithromycin combination treatment can provide positive effect in serious COVID-19 patient.^{85,86} However, hydroxychloroquine can develop significant adverse events (<10%), including prolongation of QT interval in ECG (prolongation of ventricular action potential duration), hypoglycaemia, neuropsychiatric effects, and retinopathy.^{87,88} In combination with Hydroxychloroquine azithromycin prolong QT interval. It is advisable that before initiation of these medications baseline electrocardiography (ECG) were taken to evaluate prolongation of QT interval because of the potential for arrhythmias, preferably in critically ill patients and those taking concomitant azithromycin and quinolones (QT-interval prolonging medications).⁸⁹ Hydroxychloroquine and chloroquine use is considered safe in pregnancy.⁹⁰ Future studies are needed to set out the favourable dose in COVID-19.

Umifenovir

Umifenovir (also called Arbidol hydrochloride or Arbidol) is an antiviral drug use in COV through repurposing. It develops by Pharmstandard, Russia with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting fusion of membrane in the viral envelope. Briefly, it prevents fusion of the viral membrane (hemagglutinin, a major glycoprotein) with the endosome after endocytosis. Recently, its promising candidature is accepted in China and Russia for prophylaxis and treatment of influenza.⁹¹ However, based on *in-vitro* data against SARS this drug is a candidate of interest for treating COVID-19 with a current influenza oral dose (200 mg in every 8 h) (NCT04260594, NCT04255017).⁹² Limited clinical outcome showed with Umifenovir in China for COVID-19. Anon-randomized clinical study (n=67) of COVID-19 showed that Umifenovir 9 days therapy associated with lower mortality rates (0/36) and higher discharge rates (5/31) compared with patients not receiving this drug.⁹³ This provisional data not validate the advantage of Umifenovir for COVID-19, but ongoing RCTs in China validating this agent.

Recombinant Human Angiotensin-converting Enzyme 2

Recombinant human Angiotensin-converting Enzyme 2 (rhACE2) is soluble APN01, may inhibit the entry of SARS-CoV-2 through inhibition of viral S protein from cellular interaction with the ACE2. In *in-vitro* rhACE2 impede replication of SARS-CoV-2 (1,000-5,000 times) in cell and organoids (embryonic stem cell), described in a recent study.⁹⁴ It is believed that serum angiotensin II level can decrease by the administration of rhACE2 by aside the substrate from the ACE, block additional ACE2 receptor activation and that prevent enhancement of pulmonary vascular permeability and ultimately prevent acute respiratory distress syndrome (ARDS). Further Apeiron Biologics commenced a dose-upswing, placebo controlled, double blinded trial on intravenous rhACE2 (APN01B) to access its safety and acceptability. Recently small pilot study (NCT04287686) is ongoing in China, to find out the role of rhACE2 in COVID-19 pneumonia and ARDS.⁹⁵

I. Theoretical conflict or contrasting effect of ACE inhibitors

Host cellular receptor ACE2, used by SARS-CoV-2 for its entry. This mechanism has energizing discussions on ACE inhibitors and/or angiotensin receptor blockers, whether they might treat COVID-19 or vice versa. Conflicting theoretical data available to determine whether these agents have a harmful or protective effect on patients with COVID-19. Theoretically, these drugs upregulate ACE2 receptors, which may worsen outcomes if it increases viral entry. Contrary to this, theoretically angiotensin receptor blockers may provide clinical benefit because of inhibition of ACE2 receptors. Further research, clinical trials and practice guidelines are required to test their efficacy in COVID-19. Dry, interminable cough is a major drawback associated with angiotensin converting enzyme inhibitors (ACEI) administration showed by some researcher. This drawback may attenuate by natural product noscaphine for its antitussive effect.⁹⁶

Innate Immune System enhancer

Natural Killer Cells

Boosting of innate immune responses always essential for weakening of the immune system with an increase of age. Innate immune system comprise of Natural killer (NK) cells that secures fast reaction to infection associated with virus. Macrophages and NK cells pulmonary migration perform SARS-CoV clearance mentioned in some previous report. The innate reaction prevents SARS-CoV infection for its self-capability to enhance the production of cytokines and chemokine with no help from the CD8+ T cells and

antibodies. In continuation of effort phase I trial (NCT04280224) undergoing in China, to determine inclusion of NK cells may assist for clearance of virus in pneumonia of COVID-19, completed by the end of 2020.⁹⁷

Henceforward, Green Cross Lab Cell (South Korea) and Kleo Pharmaceuticals (U.S.) mutual collaboration focus on repurposing of their NK based anti-cancer commodities to manage COVID-19. Recently, NK cells got from hematopoietic stem cell of Placenta has already developed by a USA-based company Celularity and coded as (CYNK-001).

Other cells

Cardiac cell therapy originally developed by Capricor Therapeutics, Inc comprising allogeneic cardiosphere-derived cells named CAP-1002. The cells release exosome that taken up by T cells and macrophages and restore cell through its preventive capacity. Previous preclinical data showed that this candidate prevent activation of macrophage and inhibit release of pro-inflammatory cytokines in inflammation with sepsis and autoimmune diseases. Capricor Therapeutics files IND application to the FDA, to investigate this in patients of COVID-19.⁹⁸

Recombinant Interferon

Virus-infected cells secrete type I interferons, showed a wide range antiviral action against respiratory syncytial virus (RSV), hepatitis C virus (HCV) and SARS-CoV and further, interferon β showed its antiviral capability against MERS-CoV, used alone or in combination with additional drugs.^{99, 100} IFN-alpha2b candidate recently developed by Tianjin Sinobloway Biology Trials are now ongoing to investigate their efficacy and safety in COVID-19 pneumonia (NCT04293887).

Adenovirus and Rabies virus has a viral vector to show S protein of MERS-CoV. Recombinant adenovirus (RAV) and recombinant rabies virus (RV), based vaccine showing S protein of MERS-CoV prompts intrinsic lung resident memory T-cell, secretory IgA and IgG response. Intranasal administration of RAV and RV based vaccine to BALB/c mice provide counterbalancing long-live cellular immunity and prompt antibody reaction, encouraging its defence in opposition to MERSCoV.¹⁰¹

Reducing the Inflammatory Response

Fingolimod

Oral immunomodulating agent Fingolimod structurally resemble to lipid sphingosine-1-phosphate (S1P) that primarily used for treatment of refractory multiple sclerosis. It, act as potent and competitive S1P1 receptors antagonist in lymph node T cells of. Uncontrolled immunopathogenesis may decrease by reduction of T lymphocytes associated with pulmonary influx is another approach for fingolimod. Nowits phase II trails are ended on July 2020 in First Affiliated Hospital of Fujian Medical University (NCT04280588) (n=30).¹⁰² They exclusively measure the change of pneumonia severity on X-ray images (0.5 mg OD orally, for three consecutive days).

Thalidomide

Thalidomide can inhibit synthesis of proinflammatory cytokine TNF-alpha. Thalidomide has potentially repurposed to prevent angiogenesis, inflammation, and fibrosis. Thalidomide mainly used in therapy of inflammatory Crohn syndrome and Behcet's syndrome.¹⁰³ Further, several animal studies showed its advantage in mice infected with H1N1 virus for inhibition of cytokine fabrication and inflammatory cells infiltration.¹⁰⁴ Recent researches (NCT04273529, NCT04273581) centre of attention is on immunomodulating outcome of thalidomide that might turn down injury of lung cause for SARS-CoV-2 unrestricted immune reaction.

Corticosteroids

The logic to use corticosteroids is to reduce the host inflammation associated lung injury and ARDS. However, this interest may be hindered by adverse effects, including delayed viral clearance from the respiratory tract and blood and risk of secondary infection.¹⁰⁵ Other major complication including hyperglycemia, psychosis, and a vascular necrosis are observed due to corticosteroids application.^{77, 106} A recent observational study of methylprednisolone for COVID-19 in China compare risk of death between methylprednisolone user (46 %, (23/50)) vs non user (62 %, (21/34)) with ARDS. Therefore, the adverse event and lack of proven benefit for corticosteroids put backward their routine use in patients with COVID-19. However, research has already started (NCT04273321, NCT04263402) to investigate their benefit and welfare.¹⁰⁷



Mesenchymal Stem Cells

Mesenchymal stem cell (MSCs) can impede pro-inflammatory cytokines and develop paracrine aspects need for repairing of tissues. *In-vivo* and *in-vitro* (avian influenza viruses) experimental report suggest their capacity to inhibit inflammatory infiltrate and reinstate endothelial permeability due to its immunomodulatory effect.¹⁰⁸ Now, umbilical cord and dental pulp are the source of MSCs, under trail (NCT04293692, NCT04269525, NCT04288102, NCT04302519) to explain their role in COVID-19 pneumonia.¹⁰⁹

Cyanta Therapeutics, develop MSCs based treatments based on its useful preclinical facts in lung disease and sepsis hopeful for its application against COVID-19. Recently these MSCs intravenous transplantation was prove to be effective and safe in COVID-19 pneumonia patients (n = 7) of Beijing, China. MSC transplantation quickly (2 days) improve pulmonary function and symptom of all patients and while three severe pneumonia patients after 10days recovered and discharged.¹¹⁰

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) shows various physiological effects on the immune system based upon dose dependency. IVIG in low doses capable to restore antibody deficiencies (0.2-0.5g/kg) and in a very high dose (2g/kg) it inhibits phagocytosis and proliferation inflammatory cells and obstruct cytotoxicity associated with antibody, for its immunomodulatory functions.¹¹¹ Phase II trial has already started (NCT04261426) based on the complementary effects of IVIG at a low dose (0.5g/kg for 5 days) in pneumonia of COVID-19.

SARS-CoV-2-Specific Neutralizing Antibodies or Universal CoV vaccine

Viral infections halted by antibodies mediated humoral immune response. Thus, neutralizing antibodies targeted specific surface epitope development is another perspective to treat COVID-19.¹¹² Eli Lilly, USA and AbCellera, Canada collaboratively develops an antibody to counter patient's infection associated with SARS-CoV-2. They isolated immune cells (5 million) from first phase recovered COVID-19 patient of U.S. and also point out latent anti-SARS-CoV-2 antibody sequences (greater than 500), to get the effective ones. However, they successfully develop the functional antibodies with specificity in case of the West Nile virus.¹¹³ Although this approach is a time-consuming but several companies like Vir Biotechnology, Inc. (California), Immuno Precise (Canada), Mount Sinai Health System (New York city) and Harbour BioMed (China) put their best effort to tackle SARS-CoV-2 through application of monoclonal antibodies but all of them are under preclinical stages.

CoV proteins, restoring of T cell mediated preventive responses and suppress virus. Neutralising protein induce cytolytic feedback of T cell in COVID-19. These responses inhibit S protein of virus and help to resolve infection in the host.¹¹⁴

Man-made protein monoclonal Antibody for passive immunization

Monoclonal antibodies adjunctive therapies for COVID-19 administered against inflammatory cytokines and development of innate immunity.

1. Anti-C5a Monoclonal Antibody

Complement activation (C5a bioactive molecule) takes place during acute lung injury that split from C5, responsible for the tissue injury development. C5a possess a crucial role in recruitment, and enhancement of vascular permeability pulmonary system which recruit T-lymphocytes and neutrophils. It showed that lung injury could reduce by anti-C5a therapy because of its capacity to attenuate, leakage of vascular bed and influx of neutrophil into the space of alveoli. Thus, anti-C5a monoclonal antibodies (BDB-1, IFX-1 or InflaRx), launched and, produced (Beijing Defengrei Biotechnology Co., Beijing Staidson Biopharma) targeting the physiology of inflammatory reaction that may decrease the injury of lung caused by SARS-CoV 2.¹¹⁵

2. Cytokines inhibiting monoclonal antibody

Several pro-inflammatory cytokines such as interleukins (IL-1, IL-6) and tumor necrotic factor (TNF- α), are mediator of inflammation present in the human body.¹¹⁶ The enhanced concentration of IL-6 make an interplay in mechanical ventilation.¹¹⁷ Neutrophils, monocytes and macrophages are expressed on IL-6 membrane-bound receptors (mIL-6R, CD126), responsible for inflammatory signaling. Faster reduction of lung elasticity and bronchoalveolar acute inflammation cause for increased IL-6 level. Hence, IL-6 specific inhibition is a promising tool for attenuation of inflammation associated damage.¹¹⁸

IL-6 inhibitors prevent, enhanced immune response associated with lungs and other organs damage and release of cytokine (cytokine storm).^{119,120} Earlier Chinese case series narrates IL-6 responsibility for dysregulated inflammation.¹²¹ Thus, monoclonal antibodies against IL-6 may diminish this process and improve clinical outcomes.

I. Tocilizumab

Tocilizumab approved by FDA, a monoclonal antibody act as IL-6 receptor antagonist. It follows chimeric antigen receptor T-cell therapy and use for RA treatment and cytokine release syndrome. Previous report showed that Tocilizumab at a 400mg dose improved respiratory function (91%) and increase rate of patients (n=21) discharge in COVID-19 but this study were conducted with absence of a comparator group which limits the explanation of drug specificity.¹²² Several randomized trials of tocilizumab, alone or in combination with favipiravir conducted by Chugai Pharmaceutical and Zhejiang Hisun Pharmaceutical in COVID-19 patients with severe pneumonia, are ongoing in China (NCT04310228, ChiCTR200002976).¹²³

II. Sarilumab

Sarilumab with brand name Kevzara is an IL-6 receptor antagonist already approved in treatment of RA is being investigated in a multicenter, double-blind, phase II or III trial conducted by Regeneron Pharmaceuticals and Sanofi in severe hospitalized COVID-19 patients (NCT04315298). However, its efficacy in treatment of SARS-CoV-2 is still unknown.¹²⁴

III. Bevacizumab

Vascular endothelial growth factor (VEGF) is a mediator that can prompt injury of endothelium and enhance microvascular permeability. Bevacizumab is known as a recombinant humanized monoclonal antibody with anti-VEGF specificity, capable to inhibit angiogenesis, extensively used in multiple types of cancers treatment. Now, a trial (NCT04275414) is carried out to assess the Bevacizumab efficacy in infection associated with SARS-CoV-2.¹²⁵

IV. Siltuximab

EUSA Pharma (Europe) has started his investigation to assess the Siltuximab efficacy, an anti-IL-6 monoclonal antibody for treatment of ARDS in COVID-19 patients.¹²⁷

V. Others monoclonal and polyclonal antibody

Recently Tiziana Life Sciences (UK) developed anti-IL-6 receptor antibody (TZLS-501) for a reduction in circulating IL-6 levels to treat the COVID-19 associated ARDS.¹²⁷

Eculizumab (soliris) (antibody; NCT04288713) is another monoclonal antibody inhibiting terminal complement of cytokine axis and its clinical trials are ongoing in China and its expanded phase II trial by Alexion Pharmaceuticals, USA.⁶⁸

Namilumab a whole human monoclonal antibody inhibits expression of GM-CSF, developed by Izana Bioscience, England. A small trial shows its application in treatment of COVID-19 patients before ICU admission and prior to ventilation or those are in worse condition. Its Phase III trial may start in case of an emergency.¹²⁸

Recently Celltrion Healthcare and KCDC (Korea Centers for Disease Control and prevention) mutually screen monoclonal antibodies to find the lead ones that neutralize SARS-CoV-2.

Emergent Biosolution, Maryland develops Human and Equine-derived, polyclonal hyperimmune with antibodies (COVID HIG and EIG) derived from plasma for treatment of SARS-CoV-2. It uses in severe hospitalized patients and provide immediate protection from infection. Its clinical studies are ongoing.

Human polyclonal antibodies that delivered by high-potency immunotherapy are developed by CSL Behring, USA and SAB Biotherapeutics, US against SARS-CoV-2. Its testing will start soon.¹²⁷

Table No. 2. A list of therapies and vaccines development for COVID-19

Company	Therapeutics under Trail	Vaccine under development
Gilead Sciences	Remdesivir (GS-5734)	NA
Biocryst Pharma	Galidesivir	NA
US FDA	Chloroquine	NA
Toyama Chemical	Favilavir	NA
Innovation Pharmaceuticals	Brilacidin	NA
APEIRON Biologics and University of British Columbia	APN01	NA
Roche	Actemra	NA
Regeneron	Kevzara	NA

CytoDyn	leronlimab	NA
OyaGen	OYA1	NA
Synairgen Research	SNG001	NA
Lattice Biologics	AmnioBoost	NA
Algernon Pharmaceuticals	Ifenprodil	NA
Airway Therapeutics	AT-100	NA
Cipla	LOPIMUNE	NA
Janssen Pharmaceutical	PREZCOBIX® (darunavir/cobicistat)	NA
Vir Biotechnology	Monoclonal antibodies	NA
NanoViricides	Nanoviricide® technology	NA
Takeda Pharmaceutical Company	Hyperimmune globulin (H-IG) therapy	NA
CEL-SCI	Ligand Epitope Antigen Presentation System (LEAPS) peptide immunotherapy	NA
Emergent BioSolutions	Plasma-derived product candidates	NA
Pfizer	Novel compounds for Therapy	COVID-19 vaccine
Serum Institute of India	NA	COVID-19 vaccine
Inovio Pharma	NA	INO-4700 (DNA vaccine)
Clover Biopharmaceuticals	NA	Recombinant subunit vaccine (Protein based Trimer vaccine)
Moderna and Vaccine Research Center	NA	mRNA-1273 vaccine
University of Oxford	NA	ChAdOx1 nCoV-19 (Adenovirus Vector)
Inovio Pharmaceuticals and Beijing Advaccine Biotechnology	NA	INO-4800 (DNA vaccine)
Medicago	NA	VLP Coronavirus vaccine
Altimune	NA	AdCOVID (Intranasal Nasovax platform)
Novavax	NA	NVX-CoV2373 Protein based vaccine
Tonix Pharmaceuticals	NA	TNX-1800 live modified horsepox vaccine
Entos Pharmaceuticals	NA	Fusogenix DNA vaccine
MIGAL Research Institute	NA	Avian Coronavirus Infectious Bronchitis Virus (IBV) vaccine (Protein expression vector)
Hong Kong University of Science and Technology	NA	B-cell and T-cell epitopes for Vaccine development
Zydus Cadila	NA	DNA vaccine/ recombinant measles virus vector-based vaccine
AJ Vaccines		Develop antigens that mimic the native structures of the virus

Symptomatic Control

1. Pathogen Specific Artificial Antigen- Presenting Cells or T cell immunotherapies

These are T cell therapy specifically uses in viral infection to restore natural T cell immunity. Physiologically, cancer cells and viral infections can suppress by antigen specific T cells. Thus, enormous amount of time dependent T cells and antigen specific T cells are essential to develop that start invasion of SARS-CoV-2. Immense quantities of T cells produce by transformation and proliferation of analogous effector, antigen specific cytotoxic T cells, and effector T cells activating antigen-presenting cells (aAPCs). Hence, lenti virus vector able to deliver the genetically changed aAPCs, expected to induce the T cells native to human, and that leads to ultimate proliferation and differentiation. Recently, Trials are conducting on aAPCs and its combination with cytotoxic T cells (having specificity towards antigen) to test their immunogenicity and safety issue (NCT04299724, NCT04276896). Recently, joint venture of ALLO Vir, US and Bayer College of medicine, US development T cell immunotherapies candidate, ALVR106 against influenza virus, parainfluenza virus, respiratory syncytial virus and human metapneumo virus. Now they plan to apply this agent against SARS-CoV-2. Kentucky Bio Processing (KBP) has developed a potential COVID-19 vaccine made up of COVID-19's genetic sequence cloned portion that leads to development of potential antigen under preclinical stage. It carried antigen reproduction inside the Tobacco plants and it purified further antigen after collection.⁵¹

2. Immunoglobulin or Convalescent plasma Therapy

COVID-19 potential therapy, convalescent plasma or hyperimmune immunoglobulins,¹²⁹ logic behind this treatment is that recovered patients antibodies can help infected cell viral clearance and immune clearance. They have reported several unreliable reports for convalescent plasma as rescue therapy in SARS and MERS.^{130,131} An observational trail of convalescent plasma in H1N1 influenza critically ill patients was conducted in 2009 and comparison were made in reduction of mortality between convalescent plasma receiving group (n=20) and nonreceiving group (20% vs 54.8%, $P = .01$).¹³² Theoretically, this therapy primarily provides benefits within the first 7 to 10 days of infection, when virus highly present in blood so primary immune response not developed.¹³³ Several reports describing preclinical development of a humanized monoclonal antibody against a common epitope to inhibit infection associated with SARS-CoV and SARS-COV-2. Although current commercial immunoglobulin preparations likely lack protective antibodies to SARS-CoV-2. A case series of COVID-19 in Wuhan, China, treated 3 patients with intravenous immunoglobulin at a dose of 0.3-0.5 g/kg/d for 5 days was recently published.¹³⁴ On March 24, 2020, Grifols, Spain, in collaboration with the BARDA (Biomedical Advanced Research Development Authority), apply for emergency IND (investigational new drug application) and screening donors for COVID-19 convalescent plasma or hyperimmune globulin therapy.¹³⁵ Johns Hopkins lab also starts study of antibodies obtained from plasma or serum of COVID-19 recovered people.¹³⁶

3. Vaccine

The most effective long-term strategy to prevent future outbreaks of this virus would be the development of a vaccine providing protective immunity. Genetic vaccines are easier for purification and lower costs of production as compared to conventional vaccines. Nucleic acids structure of are simple to prevent incorrect folding risk, occur in recombinant protein-based vaccines. However, key factors that impact the genetic vaccines immunogenicity are appropriate time intervals, amount of plasmid transport and administration route. We have suggested several vaccines based upon nucleic acid based on the coding sequence of S protein of SARS-CoV-2 genome.¹³⁷ However, a minimum of 12 to 18 months would be required before widespread vaccine deployment.

I. Stabilized Subunit Vaccines

Fusion needs viral glycoprotein conformational change from pre to post form. Glycoproteins are relatively unstable during pre-fusion but produce strong immune responses. Molecular clamp technology based stabilized subunit vaccine developed by a mutual collaboration of GlaxoSmithKline (GSK), CEPI and the University of Queensland, that's permit stable recombinant viral proteins in their pre-fusion form. It was also reported that molecular clamp technology based vaccines already showed their capacity in influenza virus and Ebola virus for neutralizing antibodies production and to be potent at 37°C after two weeks.¹³⁸

II. mRNA-1273

Synthetic strand of mRNA (Moderna's mRNA-1273) stabilizes viral spike protein perfusion. Thus, after IM injection, it is anticipated to elicit spike protein specific antiviral response towards SARS-CoV-2 in human bodies. It is comparatively safe than other vaccine made from inactivated pathogen and ready to be tested.¹³⁹

Self-amplifying RNA vaccine, developed by Imperial College, London within 14 days after getting the viral sequence obtained from China. It designed to inject into a muscle where it develops a new genetic code and proteins resemble to the surface of

coronavirus and express a protective immune response. The preclinical research on the animal already complete from February 10 and now plans to start clinical trials in June or July.¹⁴⁰

Two strategies employed by mRNA vaccine, production of virus-like particles (VLPs) having replica of native COVID-19 viruses and production activate immune responses after insertion in the host. In another approach mRNA are uses to express spike protein RBD of COVID-19 that induce neutralizing-antibodies in the human body. This multiple approach was applied by Fudan University, Shanghai, JiaoTong University, China and RNACure Biopharma, USA with a mixture of three genes of COVID-19 mRNA and it initiate VLPs production in co-transfect human cells. Similar vaccine developed by Medicago, Canada from the gene of SARS-CoV-2 that creates VLP. It now conducts safety and efficacy study of this vaccine on *in-vitro* and *in-vivo*. Further, its trials on human will be started in July/August, 2020.¹⁴¹

Intranasal single mRNA-T cell epitopes based vaccine adjuvant developed and repurposed by a mutual collaboration of Epivax, USA; REPROCELL, USA;CEV lab, Italy which trigger CD4 and CD8 T cell expression activated by dendritic cells. It applies these vaccines through a nasal atomizer targeted towards nasal mucosa.

Neurimmune, Switzerland and Ethris, Germany plan to develop a mRNA-based antibody taken through the inhaler and ultimately it enters the lungs of COVID-19 patients. Its clinical trial will start very soon.

li-Key or MHC class II epitope hybrid antigenic peptides are 100 times more powerful than individual peptides in immunity development. It is actually a hybrid platform for HIV. Now this platform will apply for li-Key-SARS-2 peptide developed by Genex Biotechnology (NuGenerex Immuno-Oncology) and EpiVax. Now it applies for licensing in unfamiliar countries.¹³⁹

III. ChAdOx1 nCoV-19 vaccine

Greiffex, US and University of Oxford developed this vaccine, based on S protein genetic sequence of SARS-CoV-2 with a non-replicating helper virus-independent adenovirus vector, now entered phase I/II trial (NCT04324606). It applied through an adenovirus vector which is non-replicating in nature. ACE-2 receptor chiefly expresses in the respiratory and gastrointestinal epithelium and these two main sites cover by adenovirus based vectors of SARS-CoV-2. The probability of dominant immunogenicity always preferred vector genes instead of transgenes.¹⁴²

IV. INO-4800

DNA vaccine INO-4800 developed by Inovio Pharmaceuticals, Pennsylvania and also by ImmunoPrecise Antibodies (IPA), Canada and EVQLV, New York. It comprises encoded sequences of DNA that provide antibodies against SARS-CoV-2. After delivery to human cells, it converted into proteins that produce immune responses.^{143, 144}

V. Nanoparticle-Based Vaccines

Viruses belongs to nanoscale objects therefore nanoparticles and viruses operate at the same length scale. This makes nanotechnology approaches powerful. In this technology nano fibre or nano material are applied in immunoengineering for vaccine development. Another approach to incorporate antigens is a nanoparticle-based vaccine. Through covalent bonding or encapsulation nanoparticles and epitopes of antigen form a conjugate that imitate the viruses and helpful for production and proliferation of cytokine and lymphocyte that have specificity towards antigen. Fully humanized antibodies or humanized-nanobodies can cross host cells membrane (Tran's bodies) that infected for virus and also bind to replicating proteins of virus and ultimately inhibit replication of virus. This technology applied for development of heavy-chain antibodies, variable nanobodies or single-domain antibodies (HCAbs, VH/VHHs or sdAbs) and human single-chain antibodies (Hu-scFvs) by Ablynx biopharmaceutical, Belgium. Furthermore, oral or intranasal spray mucosal vaccination not only stimulates mucosal surface immune response but also evokes systemic responses.^{145, 146} Thus, nanoparticle vaccines act as a safeguard for humans in case of respiratory viruses associated symptoms. In near future Nucleic acid based nano vaccine, Subunit nano vaccine, Peptide based nano vaccine will come into market having good stability, safety, and scalability.¹⁴⁷ Emergent BioSolutions, Washington and Novavax, Inc use antigen to isolate S protein of CoV and develop a nanoparticle vaccine, expected to provide Preliminary immunogenicity and safety results expected in July 2020. Previously this protein showed its baculovirus system stability.

VI. Other vaccine

AdCOVID is a Single-dose intranasal vaccine help to provide systemic immunity. It originally developed by a joint venture of Altimmune Inc with the University of Alabama at Birmingham (UAB) based on previous influenza platform NasoVAX™ that showed positive immunogenicity results.¹⁴⁸

Bayer College of Medicine develops a vaccine that based on recombinant protein with a receptor binding domain (RBD) of spike protein of the CoV able to bind receptor present in lung tissue of host.¹⁴⁹

CoV S-trimer protein in combination with toll-like receptor 9 (TLR9) agonist vaccine candidate developed by a joint collaboration of Clover Biopharmaceutical and Dynavax Technologies.¹⁵⁰

Hoth and Voltron Therapeutics (HaloVax), USA sign an agreement with Vaccine and Immunotherapy Center (VIC) of Massachusetts General Hospital and develop Self-Assembling Vaccine (SAV) that prevent infection in COVID-19 patients. Within the next few days this vaccine *in-vivo* testing will start. HaloVax with support from the USA Department of Defense (DOD) previously proved its utility in Lassa fever.¹⁵¹

The vaccine that expresses *Drosophila* S2 insect cell to produce 2019-nCoV viral antigens system, and capsid virus-like particle (cVLP) are applied by ExpreS²ion Biotechnologies and AdaptVac to develop vaccine antigens and test this in *in-vitro* and *in-vivo* in near future.¹⁵²

Miscellaneous Agents

Oseltamivir

Oseltamivir approved to treat influenza, a neuraminidase inhibitor, has no documented *in-vitro* activity against SARS-CoV-2. Initially, in China the COVID-19 outbreak happened during peak influenza season so a large proportion of patients received treatment of oseltamivir in combination with other drugs until SARS-CoV-2 discovery of as the cause of COVID-19.³⁵ Several clinical trials are ongoing on oseltamivir, but not as a proposed therapeutic medication.⁶⁸

Darunavir

Limited clinical outcome with darunavir has been described in China for COVID-19.¹⁵³ Randomized clinical trial (RCT) of darunavir/cobicistat in China is underway.⁶⁸

Brilacidin

It develops by Innovation Pharmaceuticals Inc in the treatment of head and neck cancer. Previous publish report suggests its inhibitory potential against Vero cells SARS-CoV-2 and it also inhibits pro-inflammatory chemokine and cytokines (IL-6). Brilacidin may act as an important candidate for the treatment of patients in COVID-19. U.S.-based virology laboratory now tests brilacidin for its antiviral efficacy.¹⁵⁴

Giapreza

Giapreza, a vasoconstrictor drug, developed by La Jolla Pharmaceutical, US. Further, this drug was again approved by the European Commission in August 2019 for adults refractory hypotension with septic shock. Adult patients with septic or other distributive shock may use Giapreza to enhance their blood pressure, but till now it is not available commercially in Europe. Probably, in the near future, it may use in an elderly patient of COVID-19 to prevent shock associated hypotension.¹⁵⁵

Ibudilast

Ibudilast (MN-166) is an orally bioavailable drug developed by MediciNova, USA. It inhibits macrophage migration inhibitory factor (MIF) and also inhibits phosphodiesterase (PDE 4 and 10). Now the clinical trial of Ibudilast has started by a collaborative effort of Yale's Advanced Therapies Group and MediciNova for COVID-19 associated acute respiratory distress syndrome (ARDS).⁶⁸

Nitazoxanide

Nitazoxanide with its safety profile has broad antiviral activity, but traditionally it used as an anthelmintic agent. It demonstrated its antiviral activity against MERS (inhibiting viral N protein) and SARS-CoV-2 (inhibiting viral S protein) in *in-vitro*. Nitazoxanide antiviral activity, safety data and immunomodulatory effect authorize its further study as used in SARS-CoV-2 therapy.¹⁵⁶

Interferon

Interferon- β showed its activity against MERS. Most published studies reported combination therapy of Interferon- β with ribavirin and/or lopinavir/ ritonavir. Similar to others, delayed treatment may limit their effectiveness.¹⁵⁷ Rebif® (interferon β -1a) originally developed by Merck KGaA, Germany and approved by FDA for treatment of multiple sclerosis. The latest guidelines of China register interferons as an alternative for combination therapy.¹⁵⁸ Now it successfully tested in COVID-19 patient of Britain.

Others

Immunomodulatory agent for noninfectious disease showed their *in-vitro* activity and supported mechanism for inhibition of SARS-CoV-2.⁵³⁻⁵⁷. However, no *in-vivo* or clinical data exist to approve their use for COVID-19.

Apilimod

Apilimod also called LAM-002. It originally developed by AI Therapeutics, USA for treatment of B-cell associated frontotemporal dementia and non-Hodgkin lymphoma. A recent report suggests that it prevents entry of SARS-CoV-2 when using alone and more effective in combination with remdesivir in *in-vitro*. Recently its IND report submitted to FDA being a hopeful drug.¹⁵⁹

Rintatolimod

Rintatolimod also called Ampligen® originally developed by AIM Immunotech having immuno modulating capacity. Argentina has approved this drug for the treatment of severe chronic fatigue syndrome. Recently clinical trial is ongoing in Netherland for treatment of pancreatic cancer patients. In collaboration with Shenzhen Smoore Technology Research, AIM Immunotech start its research in China to know efficacy of Ampligen® with smoores vaping devices for inhalation of drug deep into lungs in ARDS of COVID-19.⁶⁸

ENU200

Another repurposed oral antiviral ENU200 by Ennaid Therapeutics, GA previously approved by FDA, may block S glycoprotein and Mpro of SARS-CoV-2 and delivers specific antiviral activity. Its Phase III trial will start soon.¹⁶⁰

Indomethacin

Previous literature indicates, several DNA and RNA viruses including SARS-CoV replication halt by indomethacin. Deal with pathogenesis and replication in many viral infections Cyclooxygenases (COXs) enzyme possesses a crucial role.¹⁶¹ Indomethacin act as a COX inhibitor (Cyclopentone) having potent anti-inflammatory and analgesic properties.^{162,163}

Development of Therapeutics from a natural source

To date, the potential antiviral activity shown by several herbal medicines or their constituents. Some extracts or natural products inhibit viral replication and prove their antiviral property. Apart from plant-derived compounds, several reports also mentioned about marine natural products with their antiviral effects against different viruses. However, adequate research and development are lacking in natural products as anti-CoV agents. Such agents take part and express a crucial role for viral attack prevention which combat CoV.

Herbal Extracts

Several Chinese herbs like *Pyrrosia lingua*, *Artemisia annua*, *Lycoris radiata*, and *Lindera aggregata* extracts showed their anti-SARS-CoV effect with EC₅₀ 2.4–88.2 µg/mL (*in-vitro*).¹⁶⁴ Similarly, *Toona sinensis* aqueous leaf extract is practiced by Chinese healers as a SARS-CoV replication inhibitor, with EC₅₀ value within the range of 30–40 µg/mL.¹⁶⁵ Aqueous concentrate of *Houttuynia cordata* act as RdRp and chymotrypsin-like protease (3CLpro) inhibitor of SARS-CoV. It also enhanced cell count (CD4+ and CD8+) in *in-vitro* and *in-vivo*. It produces immune stimulatory effects, which inhibit viral replication.¹⁶⁶ However, significant inhibition produced by methanolic fractions of *Dioscorea batatas* and *Cibotium barometz* with IC₅₀ 39 and 44 µg/mL, respectively.¹⁶⁷

In addition, *Polygonum multiflorum* and *Rheum officinale*, extracts inhibited SARS-CoV spike protein (S) and host protein ACE2 with IC₅₀ 1–10 µg/mL (*In-vitro*) and proved entry into inhibitory potential.¹⁶⁸

Citrus sinensis and *Nigella sativa*, extracts reduced the reproduction of HeLa-CEACAM1a cell (HeLa-epithelial carcino-embryonic antigen-related cell adhesion molecule 1a) and infection was induced with MHV-A59 (mouse hepatitis virus-A59). It also lowered TRP gene expression but enhance intracellular calcium level. However, this effect didnot tally with the viral reproduction lowering effect. However, *Anthemis hyalina* powerfully inhibit replication of CoV.¹⁶⁹

Phyto-constituents

Previous reports suggest that a phytagglutinin named concanavalin A (molecular weight 25 kDa) found in jack beans (*Canavalia ensiformis*) actively inhibit CoV. Concanavalin A transiently inhibits, viral envelop glycoprotein hemagglutinin-esterases (HEs) and also inhibits glycosylation of membrane proteins with MIC 10 µg/mL in CoV encephalomyelitis.¹⁷⁰ So it ultimately prevents entry and replication of the virus in the host. It is restricted due to its severe hepatotoxicity in test animals.¹⁷¹ Further, bromelain a protein-

digesting enzyme from pineapple reduce CoV glycoprotein and its cell viability that isolated from pigs.¹⁶⁸ It can prevent the interaction of SARS-CoV with the host. Lycorine a chemical constituent from *Lycoris radiata* inhibited SARS-CoV with EC₅₀ 15.7 nM.¹⁶⁴ Savinin a lignans from *pterocarpus santalinus*,¹⁷² Compound isolated from *Torreya nucifera* compounds such as amentoflavone, apigenin, luteolin, and quercetin are chemically flavones and biflavones that inhibit SARS-CoV 3CLpro with IC₅₀ values of 8.3, 280.8, 20.2, and 23.8 μ M, respectively.¹⁷³ Similarly, black tea phenolic constituents such as 3-isothaeflavon-3-gallate, theaflavin-3, 30-digallate and tannic acid inhibit SARS-CoV 3CLpro with IC₅₀ value of 3, 7, and 9.5 μ M, respectively.¹⁷⁴

Omacetaxine mepissuccinate is a alkaloid isolated from *Cephalotaxus fortune* inhibit expression of human corona virus and murine with IC₅₀ ~11 nM.¹⁷⁵ From *Tylophora indica* isolated components tylophorine (IC₅₀ value of 0.018 μ M) and 7-methoxycryptopleurine (IC₅₀ 0.005 μ M) inhibit S and N protein of CoVs so inhibit their replication and prevent stomach flu associated with them.¹⁷⁶ Cepharanthine an alkaloid isolated from *Stephania cepharantha Hayata* also inhibited protease enzyme of SARS-CoV at 0.5–10 μ g/mL concentration.^{177,178} Bisbenzylisoquinoline alkaloid component berbamine extracted from the plant *Berberis amurensis* inhibits HCoV-NL63 with IC₅₀ value of 1.48 μ M.¹⁷⁹

A glucoside saikosaponins A, B2, C, and D obtained from *Scrophularia scordonia*, *Bupleurum sp.*, and *Heteromorpha sp.* within 5–25 μ M/L concentration showed their inhibitory potential in CoV-229E cells with EC₅₀ values of 8.6, 1.7, 19.9, and 13.2 μ M, respectively.¹⁸⁰ They may prevent penetration and attachment of viruses in humans. Similarly, *Isatis indigotica* phenolic components such as aloe emodin, sinigrin, hesperetin, β -sitosterol and indigo extracted from *Isatis indigotica* inhibit SARS-CoV 3CLpro with IC₅₀ 217, 752, 8.3, 365, and 1,210 μ M respectively.¹⁸¹

Salvia miltiorrhiza chemical compounds of tanshinones derived from *Salvia miltiorrhiza* such as rosmariquinone, dihydrotanshinone I and tanshinone I at 1–1000 μ M concentration inhibit SARS-CoV PLpro and 3CLpro replication and infection. However, dihydrotanshinone I inhibit with IC₅₀ 4.9 and 14.4 μ M and tanshinone I inhibit PLpro and 3CLpro with IC₅₀ 8.8 and 38.7 μ M respectively.¹⁸² Similarly, scutellarein and myricetin reduce the SARS-CoV 3CL pro effect at 10–0.01 μ M.¹⁸³

Chemical components extracted from *Broussonetia papyrifera* such as brousochalcone A, brousochalcone B, brousoflavan, kazinol(A-J), 30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavane, papyriflavonol A, and 4-hydroxyisolonchocarpin, inhibit SARS-CoV PLpro and 3CLpro. Among these components most efficient inhibition displayed by papyriflavonol A against PLpro with IC₅₀ 3.7 μ M.¹⁸⁴ Similarly, Panax ginseng component gynosaponin C also called ginsenoside Rb1 to inhibit the activity of virus at 100 μ M concentration.¹⁸⁵

The natural isolated compounds from the *Cinnamon cortex* such as cinnamtannin B1, procyanidin A2 and procyanidin B1 inhibit infection of SARS-CoV at 0–500 μ M concentration.¹⁸⁶ *Phyllanthus emblica* L. isolated polyphenolic flavonoids or carotenoid compounds such as, tetra-O-galloyl-beta-D-glucose and luteolin within 3-10 mol/L act as S protein inhibitor of SARS-Cov-2 and 3CL protease inhibitor SARS-CoV. The major limitation of luteolin is its poor oral absorption show several liposomal formulation of luteolin are developed and mix with olive pomace oil that has additional anti-inflammatory actions of its own. However, a novel luteolin analog, tetramethoxyluteolin, more potently inhibits cytokines (TNF and IL-1 β) and chemokines (CCL2 and CCL535) induced mast cells inflammation in human, need its further evaluation.¹⁸⁷

In another study, isolated compound like psoralidin, corylifol, bavachinin, neobavaisoflavone, isobavachalcone, and 4'-O-methylbavachalcone isolated from *Psoralea corylifolia* Psoralea corylifolia isolated compound like psoralidin, corylifol, bavachinin, neobavaisoflavone, isobavachalcone and 4'-O-methylbavachalcone inhibit papain-like protease of SARSCoV. Among them psoralidin showed powerful inhibition of SARS-CoV protease with IC₅₀ 4.2 μ M.¹⁸⁸ *Cassia fistula* components emodin, chrysin and rhein inhibit S protein and ACE2 of SARS-CoV in between 0–400 μ M concentration.¹⁸⁹ Although, isolated products from *Ecklonia cava* such as phlorofucofuroeckoln, eckol, dieckol, and 7-phloroeckol inhibited to porcine epidemic diarrhea virus cells with IC₅₀ values of 12.2, 22.5, 14.6 and 18.6 μ M, respectively.¹⁹⁰

Juglanin a cyclic ketone from seed husks of walnuts of *Juglans regia* blocks SARS-CoV 3a channel with IC₅₀ value of 2.3 μ M.¹⁹¹ Isolated compounds from *Paulownia mentosa* such as 30-O-methyldiplacol, 40-O-methyldiplacol, tomentin (A-E), 30-O-methyldiplacone, 40-O-methyldiplacone, 6-geranyl-40-,5,7-trihydroxy-30,50-dimethoxyflavanone, diplacone, and mimulone inhibit papain like protease (PLpro) of SARS-CoV within 0–100 μ M concentration.¹⁹² Similarly, RNA oligonucleotide nanoparticle obtained from teas components (–) galocatechin gallate and (–) catechin gallate inhibited N protein of SARS-CoV at 0.001–1 μ g/mL concentration.¹⁹³ On the other hand, isolated compounds like quercetrin, quercetin, cinanserin and rutin, from *Houttuynia cordata* at 15.63–500 μ g/mL act against murine CoV.¹⁹⁴

Fruits and twigs of *Aglaia foveolata* isolated compound sivistrol showed potent cytotoxicity against various cancer cell lines of human. This compound inhibited translation of viral mRNA of HCoV-229E at 0.6–2 μ M range with IC₅₀ of 40 nM.¹⁹⁵ Similarly, a natural phenol ferruginol having a substructure of terpenoid obtained from redwood *Sequoia sempervirens* needles showed its antitumor potential in breast, colon, and lung cancers of human and also act as significant replication inhibitor of SARS-CoV.¹⁹⁶

Isolated compounds of *Tylophora indica* (Tylophorine and 7-methoxycryptopleurine) act as CoV replication inhibitor in swine testicular cells infect with IC₅₀ 58 nM and 20 nM, respectively. Tylophorine inhibits replication of RNA and NF- κ B (JAK2-mediated) in CoV cell at 0–1000 nM concentration.¹⁹⁷

Many compounds from several species of plant like betulonic, betulinic acid, hinokinin, 8 β -hydroxyabieta-9(11),-13-dien-12-one, savinin 3 β , 12-diacetoxyabieta-6, 8, 11, 13-tetraene and curcumin act as replication inhibitors of SARS-CoV within 0–80 μ M range.¹⁹⁸ Ouabain from bovine hypothalamus acts as a viral RNA replication inhibitor (Inhibit viral clone number) within 0–3000 nM range.¹⁹⁹ Recent findings showed that lycorine (different species of Amaryllidaceae), emetine from *Cephaelis ipecacuanha* inhibit the division process of cells and also inhibit the synthesis of DNA, RNA of MERSCoV, MHV-A59HCoV-NL63 and HCoV-OC43 within 0–5 μ M concentration.¹⁷⁹

Marine alga *Halimeda tuna* produce a diterpene aldehyde component halituna, inhibit murine coronavirus.²⁰⁰ Another marine alga *Streptomyces hygroscopicus* component hygromycin B dose-dependently inhibits replication of MHV-A59 cell (mouse hepatitis virus-A59) and also inhibit necrosis based foci of the liver.²⁰¹

Bacterium *Streptomyces parvulus*, antibiotic compound actinomycin D inhibits penetration and attachment of CoV at 5–25 μ M concentration with EC₅₀ 0.02 μ M.²⁰² Mycophenolate mofetil obtained from the fungi *Penicillium brevicompactum*, *Penicillium stoloniferum*, and *Penicillium echinulatum* inhibit the division of cell and also inhibit synthesis of DNA, RNA in MERSCoV, MHV-A59, HCoV-NL63 and HCoV-OC43 in between 0–5 μ M concentration, produce immune-suppressant effect on the CoV species.¹⁷⁹

Current Treatment Procedure in COVID-19

At present specific therapy not available against COVID-19 pneumonia. Management includes transmission prevention, complications prevention, and provides supportive care. Oxygen is immediately given to patients who undergo the problem of respiratory distress (ARDS). Fluid resuscitation not required if there is no sign of hypoperfusion of tissue, as it may worsen the status of oxygen or shorten the duration of ventilation and produce lungs edema. Systemic corticosteroids are not suggested because they delay viral clearance.²⁰³

Precautionary measure taken in COVID-19

It takes several precautionary measures for patients in suspected or known COVID-19 pneumonia. All professionals of the healthcare system caring for the patient of COVID-19. It suggests respiratory and eye protection. We consider droplet precautions withdrawal. if chest radiography and successive two RT-PCR test results, from a clinically recovered patient, show negative in at least 24 h interval. However, some patient test results show negative but a few days later, test results show positive consideration as viral carriers.²⁰⁴ Thus the decision for droplet precautions against withdrawal depends on judgments and evaluation of clinicians, but not dependent on clinical, laboratory and radiological confirmation. Although asymptomatic patients close contact were not infected but quite regarded as viral carriers. The COVID-19 pneumonia infected cases are infectious before the disease onset and after treatment. Thus, there is a need to re-evaluate the hospital discharge norms and quarantine norms to achieve adequate disease control.

Recommendations in COVID-19

Recently, March 13, 2020 WHO clinical management guidance document or Centers for Disease Control and Prevention highlight the importance of supportive therapy/care based on intensity of illness, ranging from symptomatic treatment for mild disease cases to ventilatory management for ARDS and early identification and treatment of viral infections and sepsis in critically ill patients. Further, it also states that still now available COVID-19 treatment has no specificity. Corticosteroids are avoided or not routinely given. Investigational therapeutics, specifically remdesivir, is mentioned as options through either ongoing clinical trials or compassionate use. Based upon this, the WHO recently declare to launch a worldwide “mega trial” called SOLIDARITY.²⁰⁵ It is a realistic trial design that will randomly use in confirmed cases with standard care of lopinavir and ritonavir combination alone or lopinavir and ritonavir combination with remdesivir or lopinavir and ritonavir combination with interferon- β and use of chloroquine or hydroxychloroquine. In this trail, drug application mainly based on locally available drugs.

Although, pharmacological or clinical management is important in COVID-19 but now self-isolation, social distancing, wearing of mask and development of self-immunity by nutraceuticals with yoga and pranayam are other parameter to prevent COVID19. We conclude it that quick epidemiologic tracking, diagnostic testing and preventive development and appropriate therapeutic strategies are required for SARS-CoV-2 viral genome.

Limitation and Conclusion

This review has several limitations, like Few clinical trials mentioned, mostly comprises descriptive reports and case series from China and other countries affected early in this pandemic recommendations thus relevant international data could lack and research findings are constantly developing as fresh evidence arises. Further, the treatment data to date derive from small clinical trials (not over 250 patients). There is bias of treatment effect. It mainly focused only on adult patients but may not apply for a pediatric patient. Outcomes including fatality case-rates must be clarified. This paper addressed numerous aspects concerning nCOVID-19 and its interaction with other coronavirus diseases, and the function of various approaches in the control and prevention of nCOVID-19. In particular, there are actually no COVID-19 vaccines or unique antiviral medicines. All the medications prescribed come from information gained during the diagnosis of MERS, SARS or other coronavirus families. More analysis is required to show the efficacy of such medicines.

Acknowledgements:

We are thankful to Myongji University, South Korea.

Consent for Publication:

We, hereby, declare that we participated in the study and development of this manuscript. We give consent this manuscript for publication.

Funding:

This study has not received any external funding.

Ethical approval

Not applicable.

Conflict of Interest:

The authors declare that there are no conflicts of interests.

Peer-review:

External peer-review was done through double-blind method.

Data and materials availability:

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*. 2020; 382(8): 727-733.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020; 395(10223): 497-506.
3. WHO. (2020). Situation Report –39, February 28th 2020. Retrieved from <https://www.who.int/docs/default-source/coronaviruse/situationreports/20200228-sitrep-39-covid-19.pdf>.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Yu T. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020; 395(10223):507-13.
5. Tu YF, Chien CS, Yarmishyn AA, Lin YY, Luo YH, Lin YT, Lai WY, Yang DM, Chou SJ, Yang YP, Wang ML. A review of SARS-CoV-2 and the ongoing clinical trials. *International journal of molecular sciences*. 2020; 21(7):2657.
6. Li F. Structure, function, and evolution of coronavirus spike proteins. *Annual review of virology*. 2016; 3:237-61.
7. Yang P, Wang X. COVID-19: a new challenge for human beings. *Cellular & molecular immunology*. 2020; 17(5):555-7.
8. Woo PC, Lau SK, Huang Y, Yuen KY. Coronavirus diversity, phylogeny and interspecies jumping. *Experimental Biology and Medicine*. 2009; 234(10):1117-27.
9. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nature Reviews Microbiology*. 2016; 14(8):523.
10. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH,



- Nitsche A, Müller MA. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020; 181, 271–280.
11. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature medicine*. 2005; 11(8):875–879.
 12. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proceedings of the National Academy of Sciences*. 2009; 106(14):5871–5876.
 13. Baranov PV, Henderson CM, Anderson CB, Gesteland RF, Atkins JF, Howard MT. Programmed ribosomal frameshifting in decoding the SARS-CoV genome. *Virology*. 2005 Feb 20; 332(2):498–510.
 14. Mielech AM, Chen Y, Mesecar AD, Baker SC. Nidovirus papain-like proteases: multifunctional enzymes with protease, deubiquitinating and delSGylating activities. *Virus research*. 2014; 194:184–90.
 15. Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LL, Guan Y, Rozanov M, Spaan WJ, Gorbalenya AE. Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineages. *Journal of molecular biology*. 2003 Aug 29; 331(5):991–1004.
 16. Krijnse-Locker J, Ericsson M, Rottier PJ, Griffiths G. Characterization of the budding compartment of mouse hepatitis virus: evidence that transport from the RER to the Golgi complex requires only one vesicular transport step. *The Journal of cell biology*. 1994; 124(1):55–70.
 17. Siu YL, Teoh KT, Lo J, Chan CM, Kien F, Escriou N, Tsao SW, Nicholls JM, Altmeyer R, Peiris JS, Bruzzone R. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. *Journal of virology*. 2008; 82(22):11318–30.
 18. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses*. 2012 Jun; 4(6):1011–33.
 19. Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, Wong BH, Poon RW, Cai JJ, Luk WK, Poon LL. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *Journal of virology*. 2005; 79(2):884–95.
 20. Van Der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, Wertheim-van Dillen PM, Kaandorp J, Spaargaren J, Berkhout B. Identification of a new human coronavirus. *Nature medicine*. 2004; 10(4):368–73.
 21. Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. *Journal of clinical medicine*. 2020; 9(2):575.
 22. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*. 2020 Apr 30; 382(18):1708–20.
 23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020; 395(10223):497–506.
 24. van Boheemen S, de Graaf M, Lauber C, Bestebroer TM, Raj VS, Zaki AM, Osterhaus AD, Haagmans BL, Gorbalenya AE, Snijder EJ, Fouchier RA. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. *MBio*. 2012; 3(6).
 25. Woo PC, Lau SK, Li KS, Tsang AK, Yuen KY. Genetic relatedness of the novel human group C betacoronavirus to Tylonycteris bat coronavirus HKU4 and Pipistrellus bat coronavirus HKU5. *Emerging microbes & infections*. 2012; 1(1):1–5.
 26. Woo PC, Wang M, Lau SK, Xu H, Poon RW, Guo R, Wong BH, Gao K, Tsoi HW, Huang Y, Li KS. Comparative analysis of twelve genomes of three novel group 2c and group 2d coronaviruses reveals unique group and subgroup features. *Journal of virology*. 2007; 81(4):1574–85.
 27. van Boheemen S, de Graaf M, Lauber C, Bestebroer TM, Raj VS, Zaki AM, Osterhaus AD, Haagmans BL, Gorbalenya AE, Snijder EJ, Fouchier RA. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. *MBio*. 2012;3(6):1–9.
 28. Woo PC, Lau SK, Li KS, Tsang AK, Yuen KY. Genetic relatedness of the novel human group C betacoronavirus to Tylonycteris bat coronavirus HKU4 and Pipistrellus bat coronavirus HKU5. *Emerging microbes & infections*. 2012; 1(1):1–5.
 29. Lam TT, Shum MH, Zhu HC, Tong YG, Ni XB, Liao YS, Wei W, Cheung WY, Li WJ, Li LF, Leung GM. Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China. *BioRxiv*. 2020:1–20.
 30. Spiegel M, Schneider K, Weber F, Weidmann M, Hufert FT. Interaction of severe acute respiratory syndrome-associated coronavirus with dendritic cells. *Journal of general virology*. 2006; 87(7):1953–60.
 31. Zhao J, Zhao J, Legge K, Perlman S. Age-related increases in PGD 2 expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice. *The Journal of clinical investigation*. 2011; 121(12):4921–30.

32. Zhao J, Zhao J, Perlman S. T cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice. *Journal of virology*. 2010; 84(18):9318-25.
33. Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *New England Journal of Medicine*. 2020; 382(16):1564-7.
34. Toosy AH, O'sullivan S. An overview of middle east respiratory syndrome in the middle east. *Fowler's Zoo and Wild Animal Medicine Current Therapy*, Volume 9. 2019:287.
35. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *Jama*. 2020; 323(11):1061-9.
36. Hindson J. COVID-19: faecal-oral transmission?. *Nature Reviews Gastroenterology & Hepatology*. 2020; 17(5):259.
37. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging microbes & infections*. 2020; 9(1):221-36.
38. Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infection, Genetics and Evolution*. 2020; 79:104212.
39. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, Guo Q, Sun X, Zhao D, Shen J, Zhang H. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nature medicine*. 2020; 26(4):502-5.
40. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Hu Y, Li Y. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. 2020
41. Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus disease 2019 (COVID-19): a perspective from China. *Radiology*. 2020; 296 (2):15-25.
42. Malainou, C.; Herold, S. Influenza. *Internist* 2019, 60, 1127–1135.
43. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nature Reviews Microbiology*. 2016; 14(8):523-534.
44. Zumla A, Hui DS. Emerging and reemerging infectious diseases: global overview. *Infectious Disease Clinics*. 2019 Dec 1; 33(4): xiii-xiix.
45. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clinical microbiology reviews*. 2015; 28(2):465-522.
46. Chan JF, Li KS, To KK, Cheng VC, Chen H, Yuen KY. Is the discovery of the novel human betacoronavirus 2c EMC/2012 (HCoV-EMC) the beginning of another SARS-like pandemic?. *Journal of Infection*. 2012; 65(6):477-89.
47. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology*. 2020:200370.
48. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, Cui J, Xu W, Yang Y, Fayad ZA, Jacobi A. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology*. 2020; 295(1):202-207.
49. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, Ling Y, Jiang Y, Shi Y. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology*. 2020; 295(1):210-217.
50. Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, Hu Q, Xia L. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *European radiology*. 2020:1-4.
51. Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, Xu H. Positive RT-PCR test results in patients recovered from COVID-19. *Jama*. 2020 Apr 21; 323(15):1502-3.
52. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). *Clinical Infectious Diseases*. 2020; 1-8.
53. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci. Trends* (2020).
54. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature communications*. 2020; 11(1):1-4.
55. Pillaiyar T, Meenakshisundaram S, Manickam M. Recent discovery and development of inhibitors targeting coronaviruses. *Drug discovery today*. 2020; 25(4):668-88.
56. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β -mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochemical Journal*. 2012; 443(3):851-856.
57. Yang SN, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β 1 heterodimer. *Antiviral research*. 2020:104760: 1-26.

58. Caly L, Wagstaff KM, Jans DA. Nuclear trafficking of proteins from RNA viruses: potential target for antivirals?. *Antiviral research*. 2012; 95(3):202-206.
59. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral research*. 2020 Apr 3:104787 (1-4).
60. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004 Mar 1; 59(3):252-6.
61. De Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, Van Nieuwkoop S, Bestebroer TM, Van Den Hoogen BG, Neyts J, Snijder EJ. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrobial agents and chemotherapy*. 2014 Aug 1; 58(8):4875-84.
62. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, Li F, Xiao C, Gao H, Yu P, Cai JP. Treatment with lopinavir/ritonavir or interferon- β 1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *The Journal of infectious diseases*. 2015; 212(12):1904-13.
63. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MM, Tse MW, Que TL, Peiris JS, Sung J, Wong VC. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong medical journal*. 2003;9(6):399-406.
64. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, Smith EC, Case JB, Feng JY, Jordan R, Ray AS. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *MBio*. 2018 May 2; 9(2):1-15.
65. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—A possible reference for coronavirus disease-19 treatment option. *Journal of medical virology*. 2020; 92(6):556-63.
66. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. Accessed March 18, 2020.
67. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*. 2020; 1787-1799.
68. ClinicalTrials.gov. Accessed March 18, 2020. <https://clinicaltrials.gov/>
69. Uno Y. Camostat mesilate therapy for COVID-19. *Internal and Emergency Medicine*. 2020 Apr 29:1-2.
70. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, Neville S, Carra E, Lew W, Ross B, Wang Q. Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo [2, 1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses.
71. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. *Travel medicine and infectious disease*. 2020 Mar 5:101615.
72. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research*. 2020; 30(3):269-71.
73. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature communications*. 2020; 11(1):1-4.
74. World Health Organization. WHO R&D blueprint: ad-hoc expert consultation on clinical trials for Ebola therapeutics. Published October 2018. Accessed March 20, 2020. <https://www.who.int/ebola/drc-2018/summaries-of-evidenceexperimental-therapeutics.pdf>
75. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proceedings of the Japan Academy, Series B*. 2017; 93(7):449-63.
76. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Zhang J, Yin P. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. *MedRxiv*. 2020 Jan 1.
77. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006 Sep 12; 3(9):e343.
78. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, Jose J, Alraddadi B, Almotairi A, Al Khatib K, Abdulmomen A. Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study. *Clinical infectious diseases*. 2020 Apr 15; 70(9):1837-44.
79. Altinbas S, Holmes JA, Altinbas A. Hepatitis C Virus Infection in Pregnancy: An Update. *Gastroenterology Nursing*. 2020; 43(1):12-21.
80. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. *The Lancet infectious diseases*. 2003; 3(11):722-727.
81. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *Journal of Antimicrobial Chemotherapy*. 2020 Mar 20.



82. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *International journal of antimicrobial agents*. 2020 Mar 12;105938.
83. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*. 2020; 71:732-739.
84. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends*. 2020: P1-P2. DOI: 10.5582/bst.2020.01047
85. Gautret P, Lagier JC, Parola P, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honoré S. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International journal of antimicrobial agents*. 2020 Mar 20;105949.
86. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci)*. Published online March 6, 2020. doi:10.3785/j.issn.1008-9292.2020.03.03
87. Kalil AC. Treating COVID-19—off-label drug use, compassionate use, and randomized clinical trials during pandemics. *Jama*. 2020 May 19; 323(19):1897-8.
88. Interview with David Juurlink. Coronavirus (COVID-19) update: chloroquine/hydroxychloroquine and azithromycin. *JAMA*. March 24, 2020.
89. Chloroquine [database online]. Hudson, OH: Lexicomp Inc; 2016. Accessed March 17, 2020.<http://online.lexi.com>
90. Osadchy A, Ratnapalan T, Koren G. Ocular toxicity in children exposed in utero to antimalarial drugs: review of the literature. *The Journal of rheumatology*. 2011; 38(12):2504-8.
91. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proceedings of the National Academy of Sciences*. 2017; 114(2):206-14.
92. Khamitov RA, Loginova S, Shchukina VN, Borisevich SV, Maksimov VA, Shuster AM. Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures. *Voprosy virusologii*. 2008; 53(4):9-13.
93. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clinical infectious diseases*. 2020 Mar 16.
94. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Del Pozo CH, Prosper F, Romero JP. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell*. 2020 Apr 24.
95. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hards K. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Critical care*. 2017; 21(1):1-9.
96. Ebrahimi SA. Noscipine, a possible drug candidate for attenuation of cytokine release associated with SARS-CoV-2. *Drug Development Research*. 2020;1-3.
97. Chen J, Lau YF, Lamirande EW, Paddock CD, Bartlett JH, Zaki SR, Subbarao K. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. *Journal of virology*. 2010 Feb 1; 84(3):1289-301.
98. Gimona M, Pachler K, Laner-Plamberger S, Schallmoser K, Rohde E. Manufacturing of human extracellular vesicle-based therapeutics for clinical use. *International journal of molecular sciences*. 2017 Jun; 18(6):1190 (1-19).
99. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. *The Lancet*. 2003; 362(9380):293-4.
100. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature communications*. 2020 Jan 10; 11(1):1-4.
101. Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, Wang ZH, Tebbutt SJ, Kollmann TR, Fish EN. Interferon- α 2b Treatment for COVID-19. *Frontiers in Immunology*. 2020 May 15; 11:1061.
102. Pelletier D, Hafler DA. Fingolimod for multiple sclerosis. *New England Journal of Medicine*. 2012; 366(4):339-47.
103. Vargesson N. Thalidomide-induced teratogenesis: History and mechanisms. *Birth Defects Research Part C: Embryo Today: Reviews*. 2015; 105(2):140-56.
104. Zhu H, Shi X, Ju D, Huang H, Wei W, Dong X. Anti-inflammatory effect of thalidomide on H1N1 influenza virus-induced pulmonary injury in mice. *Inflammation*. 2014 Dec 1;37(6):2091-8.
105. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet*. 2020; 395(10223):473-5.
106. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, Jose J, Pinto R, Al-Omari A, Kharaba A, Almotairi A. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome.

- American journal of respiratory and critical care medicine. 2018 Mar 15; 197(6):757-67.
107. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA internal medicine*. 2020 Mar 13.
 108. Lee JW, Gupta N, Serikov V, Matthay MA. Potential application of mesenchymal stem cells in acute lung injury. *Expert opinion on biological therapy*. 2009; 9(10):1259-70.
 109. Li Y, Xu J, Shi W, Chen C, Shao Y, Zhu L, Lu W, Han X. Mesenchymal stromal cell treatment prevents H9N2 avian influenza virus-induced acute lung injury in mice. *Stem cell research & therapy*. 2016 Dec 1; 7(1):159.
 110. Chrzanowski W, Kim SY, McClements L. Can Stem Cells Beat COVID-19: Advancing Stem Cells and Extracellular Vesicles Toward Mainstream Medicine for Lung Injuries Associated With SARS-CoV-2 Infections. *Frontiers in Bioengineering and Biotechnology*. 2020; 8:554.
 111. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clinical and experimental immunology*. 2005; 142(1):1.
 112. Zhou G, Zhao Q. Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. *International Journal of Biological Sciences*. 2020; 16(10):1718.
 113. Tsioris K, Gupta NT, Ogunniyi AO, Zimnisky RM, Qian F, Yao Y, Wang X, Stern JN, Chari R, Briggs AW, Clouser CR. Neutralizing antibodies against West Nile virus identified directly from human B cells by single-cell analysis and next generation sequencing. *Integrative Biology*. 2015 Dec 30; 7(12):1587-97.
 114. Philippidis A. In Praise of Lesser-Sung Life Sciences Clusters: Across the country—not just in Boston and San Francisco—work on cell and gene therapies, coronavirus vaccines and drugs, and other boons continues apace. *Genetic Engineering & Biotechnology News*. 2020 Jun 1; 40(6):46-9.
 115. Guo RF, Ward PA. Role of C5a in inflammatory responses. *Annu. Rev. Immunol.* 2005; 23:821-52.
 116. Voiriot G, Razazi K, Amsellem V, Van Nhieu JT, Abid S, Adnot S, Dessap AM, Maitre B. Interleukin-6 displays lung anti-inflammatory properties and exerts protective hemodynamic effects in a double-hit murine acute lung injury. *Respiratory research*. 2017 Dec 1; 18(1):64.
 117. Herold TV, Arnreich C, Hellmuth JC, von Bergwelt-Baildon M, Klein M, Weinberger T. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. *medRxiv* 2020. Google Scholar. 2020.
 118. Rose-John S, Waetzig GH, Scheller J, Grötzinger J, Seegert D. The IL-6/sIL-6R complex as a novel target for therapeutic approaches. *Expert opinion on therapeutic targets*. 2007; 11(5):613-24.
 119. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *International journal of biological sciences*. 2012; 8(9):1237.
 120. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, HLH Across Speciality Collaboration. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*. 2020 Mar 28; 395(10229):1033.
 121. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet*. 2020 Mar 11.
 122. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X. Effective treatment of severe COVID-19 patients with tocilizumab. *Proceedings of the National Academy of Sciences*. 2020 May 19; 117(20):10970-5.
 123. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. Accessed March 18, 2020. <https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf>
 124. Sanofi. Sanofi and Regeneron begin global Kevzara (sarilumab) clinical trial program in patients with severe COVID-19 [news release]. Published March 16, 2020. Accessed March 18, 2020.
 125. Thickett DR, Armstrong L, Christie SJ, Millar AB. Vascular endothelial growth factor may contribute to increased vascular permeability in acute respiratory distress syndrome. *American journal of respiratory and critical care medicine*. 2001 Nov 1; 164(9):1601-5.
 126. Tu YF, Chien CS, Yarmishyn AA, Lin YY, Luo YH, Lin YT, Lai WY, Yang DM, Chou SJ, Yang YP, Wang ML. A review of SARS-CoV-2 and the ongoing clinical trials. *International journal of molecular sciences*. 2020 Jan; 21(7):2657.
 127. Philippidis A. COVID-19: Top 60 Drug Treatments in Development: The biopharma industry is ramping up the development of dozens of potential drug therapies and clinical testing in an all-hands effort to combat the pandemic. *Genetic Engineering & Biotechnology News*. 2020 Apr 1; 40(4):10-3.
 128. Mehta P, Porter JC, Manson JJ, Isaacs JD, Openshaw PJ, McInnes IB, Summers C, Chambers RC. Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities. *The Lancet Respiratory Medicine*. 2020 Jun 16.

129. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *The Lancet Infectious Diseases*. 2020; 20(4):398-400.
130. Soo YO, Cheng Y, Wong R, Hui DS, Lee CK, Tsang KK, Ng MH, Chan P, Cheng G, Sung JJ. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clinical microbiology and infection*. 2004 Jul;10(7):676-8.
131. Arabi Y, Balkhy H, Hajeer AH, Bouchama A, Hayden FG, Al-Omari A. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *Springerplus*. 2015; 4: 709. Table. Candidate therapies for the management of Coronavirus Disease-19 a Drug Proposed mechanism of action Evidence for SARS-CoV-2 Clinical trials. 2015;28.
132. Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, Liu R, Watt CL, Chan WM, Lai KY, Koo CK. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clinical Infectious Diseases*. 2011 Feb 15; 52(4):447-56.
133. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *Jama*. 2020 Apr 28; 323(16):1582-9.
134. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, Han Y, Lin L, Ruan L, Li T. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *InOpen forum infectious diseases* 2020 Mar (Vol. 7, No. 3, p. ofaa102). US: Oxford University Press.
135. US Food and Drug Administration. Investigational COVID-19 Convalescent plasma: emergency INDs. Updated April 3, 2020. <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process/investigational-covid-19-convalescent-plasma-emergency-ind>
136. Wang C, Li W, Drabek D, Okba NM, van Haperen R, Osterhaus AD, van Kuppeveld FJ, Haagmans BL, Grosveld F, Bosch BJ. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nature communications*. 2020 May 4; 11(1):1-6.
137. Pandey SC, Pande V, Sati D, Upreti S, Samant M. Vaccination strategies to combat novel corona virus SARS-CoV-2. *Life Sciences*. 2020 Jun 12:117956.
138. Chappell K, Watterson D, Young P. Rapid response pipeline for stabilized subunit vaccines. In *Proceedings of the Vaccine Technology VII*, Mont Tremblant, QC, Canada, 17–22 June 2018.
139. Moderna. Moderna announces funding award from CEPI to accelerate development of messenger RNA (mRNA) vaccine against novel coronavirus; 2020. [accessed 2020 Feb 15].
140. McKay PF, Hu K, Blakney AK, Samnuan K, Brown JC, Penn R, Zhou J, Bouton CR, Rogers P, Polra K, Lin PJ. Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine candidate induces high neutralizing antibody titers in mice. *Nature communications*. 2020 Jul 9; 11(1):1-7.
141. Rosales-Mendoza S, Márquez-Escobar VA, González-Ortega O, Nieto-Gómez R, Arévalo-Villalobos JL. What does plant-based vaccine technology offer to the fight against COVID-19? *Vaccines*. 2020 Jun; 8(2):183.
142. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, Smith EC, Case JB, Feng JY, Jordan R, Ray AS. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *MBio*. 2018 May 2; 9(2): e00221-18 (1-15).
143. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature communications*. 2020; 11(1):1-4.
144. Lee JW, Gupta N, Serikov V, Matthay MA. Potential application of mesenchymal stem cells in acute lung injury. *Expert opinion on biological therapy*. 2009; 9(10):1259-70.
145. Al-Halifa S, Gauthier L, Arpin D, Bourgault S, Archambault D. Nanoparticle-based vaccines against respiratory viruses. *Frontiers in immunology*. 2019 Jan 24; 10:22: 1-12.
146. Chan WC. Nano Research for COVID-19. *ACS nano*. 2020 Mar 31.
147. Shin MD, Shukla S, Chung YH, Beiss V, Chan SK, Ortega-Rivera OA, Wirth DM, Chen A, Sack M, Pokorski JK, Steinmetz NF. COVID-19 vaccine development and a potential nanomaterial path forward. *Nature Nanotechnology*. 2020:1-0.
148. Katual MK, Singh G, Harikumar SL. Current trends and epidemiology on novel covid-19: Pandemic. *Journal of Education Technology in Health Sciences*. 2020; 7(1):3-13.
149. Mukherjee S. The first coronavirus drug candidate is set for testing in China. *Fortune*. 2020.
150. Clover Biopharmaceuticals. Clover initiates development of recombinant subunit-trimer vaccine for Wuhan coronavirus (2019-nCoV). 2020.
151. Hoth Therapeutics Announces Agreement to Joint Development for a Self Assembling Vaccine (SAV) for the Potential Prevention of the Coronavirus (COVID-19) | Vaccines | News Channels [Internet]. [Cited 2020 Apr 20]. Available from: <https://pipelinereview.com/index.php/2020/03/23/74080>



152. de Jongh WA, Salgueiro S, Dyring C. The use of *Drosophila* S2 cells in R&D and bioprocessing. *Pharm Bioprocess*. 2013 Jun; 1(2):197-213.
153. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther*. 2020; 14 (1): 58-60.
154. Brilacidin. Available online: <http://www.ipharminc.com/brilacidin-1>.
155. La Jolla Pharmaceutical. La Jolla Pharmaceutical Company to provide GIAPREZA (angiotensin II) in Italy for compassionate use in patients with septic shock associated with COVID-19. <https://lajollapharmaceutical.com/wp-content/uploads/2020/03/GIAPREZA-Compassionate-Use-FINAL.pdf>.
156. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. *Journal of infection and public health*. 2016 May 1; 9(3):227-30.
157. Morra ME, Van Thanh L, Kamel MG, Ghazy AA, Altibi AM, Dat LM, Thy TN, Vuong NL, Mostafa MR, Ahmed SI, Elabd SS. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. *Reviews in medical virology*. 2018; 28(3):e1977.
158. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. <https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf>.
159. Gil C, Ginex T, Maestro I, Nozal V, Barrado-Gil L, Cuesta-Geijo MA, Urquiza J, Ramírez D, Alonso C, Campillo NE, Martínez A. COVID-19: Drug targets and potential treatments. *Journal of Medicinal Chemistry*. 2020 Jun 8; (A-AB).
160. Kumari P, Rawat K, Saha L. Pipeline Pharmacological Therapies in Clinical Trial for COVID-19 Pandemic: a Recent Update. *Current Pharmacology Reports*. 2020 Jul 18:1-3.
161. Raaben M, Einerhand AWC, Taminiau LJA, Van Houdt M, Bouma J, Raatgeep RH, Büller HA, de Haan CAM, Rossen JWA. Cyclooxygenase activity is important for efficient replication of mouse hepatitis virus at an early stage of infection. *Virology Journal*. 2007, 4, 55.
162. Vane JR, Botting RM, Mechanism of action of nonsteroidal anti-inflammatory drugs. *American Journal of Medicine*. 1998, 104, 2S-22S
163. Amici C, Di Caro A, Ciucci A, Chiappa L, Castillett C, Martella V, Decaro N, Buonavoglia C, Capobianchi MR, Santoro MG, Indomethacin has a potent antiviral activity against SARS coronavirus. *Antiviral Therapy*. 2006, 11, 1021-1030
164. Li SY, Chen C, Zhang HQ, Guo HY, Wang H, Wang L, Zhang X, Hua SN, Yu J, Xiao PG, Li RS. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antiviral research*. 2005 Jul 1; 67(1):18-23.
165. Chen CJ, Michaelis M, Hsu HK, Tsai CC, Yang KD, Wu YC, Cinatl Jr J, Doerr HW. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. *Journal of ethnopharmacology*. 2008 Oct 30; 120(1):108-11.
166. Lau KM, Lee KM, Koon CM, Cheung CS, Lau CP, Ho HM, Lee MY, Au SW, Cheng CH, Bik-San Lau C, Tsui SK. Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. *Journal of Ethnopharmacology*. 2008; 118(1):79-85.
167. Wen CC, Shyur LF, Jan JT, Liang PH, Kuo CJ, Arulselvan P, Wu JB, Kuo SC, Yang NS. Traditional Chinese medicine herbal extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication. *Journal of traditional and complementary medicine*. 2011; 1(1):41-50.
168. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral research*. 2007; 74(2):92-101.
169. Ulasli M, Gurses SA, Bayraktar R, Yumrutas O, Oztuzcu S, Igci M, Igci YZ, Cakmak EA, Arslan A. The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. *Molecular biology reports*. 2014; 41(3):1703-11.
170. Greig AS, Bouillant AM. Binding effects of concanavalin A on a coronavirus. *Canadian Journal of Comparative Medicine*. 1977; 41(1):122.
171. Mitchell CA, Ramessar K, O'Keefe BR. Antiviral lectins: Selective inhibitors of viral entry. *Antiviral research*. 2017 Jun 1; 142:37-54.
172. Wen CC, Kuo YH, Jan JT, Liang PH, Wang SY, Liu HG, Lee CK, Chang ST, Kuo CJ, Lee SS, Hou CC. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *Journal of medicinal chemistry*. 2007; 50(17):4087-95.
173. Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY, Kim D, Nguyen TT, Park SJ, Chang JS, Park KH, Rho MC. Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition. *Bioorganic & medicinal chemistry*. 2010; 18(22):7940-7.
174. Chen CN, Lin CP, Huang KK, Chen WC, Hsieh HP, Liang PH, Hsu JT. Inhibition of SARS-CoV 3C-like protease activity by theaflavin-3, 3'-digallate (TF3). *Evidence-Based Complementary and Alternative Medicine*. 2005 Jun 1; 2(2) 209-215.

175. Li H, Wen Y, Wang F, Wu P, Wei X. Cephalofortunone, a structurally unique Cephalotaxus alkaloid from Cephalotaxus fortune Hook. f. Tetrahedron Letters. 2015; 56(42):5735-7.
176. Yang CW, Lee YZ, Kang IJ, Barnard DL, Jan JT, Lin D, Huang CW, Yeh TK, Chao YS, Lee SJ. Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. Antiviral research. 2010; 88(2):160-8.
177. Zhang CH, Wang YF, Liu XJ, Lu JH, Qian CW, Wan ZY, Yan XG, Zheng HY, Zhang MY, Xiong S, Li JX. Antiviral activity of cepharanthine against severe acute respiratory syndrome coronavirus in vitro. Chinese medical journal. 2005; 118(6):493-6.
178. Kim DE, Min JS, Jang MS, Lee JY, Shin YS, Park CM, Song JH, Kim HR, Kim S, Jin YH, Kwon S. Natural bis-benzylisoquinoline alkaloids-tetrandrine, fangchinoline, and cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells. Biomolecules. 2019 (11):696.
179. Shen L, Niu J, Wang C, Huang B, Wang W, Zhu N, Deng Y, Wang H, Ye F, Cen S, Tan W. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. Journal of virology. 2019; 93(12):1-15.
180. Cheng PW, Ng LT, Chiang LC, Lin CC. Antiviral effects of saikosaponins on human coronavirus 229E in vitro. Clinical and Experimental Pharmacology and Physiology. 2006; 33(7):612-6.
181. Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY, Hsieh CC, Chao PD. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral research. 2005 Oct 1; 68(1):36-42.
182. Park JY, Kim JH, Kim YM, Jeong HJ, Kim DW, Park KH, Kwon HJ, Park SJ, Lee WS, Ryu YB. Tanshinones as selective and slow-binding inhibitors for SARS-CoV cysteine proteases. Bioorganic & medicinal chemistry. 2012; 20(19):5928-35.
183. Yu MS, Lee J, Lee JM, Kim Y, Chin YW, Jee JG, Keum YS, Jeong YJ. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorganic & medicinal chemistry letters. 2012; 22(12):4049-54.
184. Park JY, Yuk HJ, Ryu HW, Lim SH, Kim KS, Park KH, Ryu YB, Lee WS. Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. Journal of enzyme inhibition and medicinal chemistry. 2017; 32(1):504-12.
185. Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YS, Hsu HH, Huang HC, Wu D, Brik A, Liang FS. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proceedings of the National Academy of Sciences. 2004; 101(27):10012-7.
186. Zhuang M, Jiang H, Suzuki Y, Li X, Xiao P, Tanaka T, Ling H, Yang B, Saitoh H, Zhang L, Qin C. Procyanidins and butanol extract of Cinnamomi Cortex inhibit SARS-CoV infection. Antiviral research. 2009; 82(1):73-81.
187. Yi L, Li Z, Yuan K, Qu X, Chen J, Wang G, Zhang H, Luo H, Zhu L, Jiang P, Chen L. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. Journal of virology. 2004; 78(20):11334-9.
188. Kim DW, Seo KH, Curtis-Long MJ, Oh KY, Oh JW, Cho JK, Lee KH, Park KH. Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia. Journal of enzyme inhibition and medicinal chemistry. 2014; 29(1):59-63.
189. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral research. 2007; 74(2):92-101.
190. Kwon HJ, Ryu YB, Kim YM, Song N, Kim CY, Rho MC, Jeong JH, Cho KO, Lee WS, Park SJ. In vitro antiviral activity of phlorotannins isolated from Ecklonia cava against porcine epidemic diarrhea coronavirus infection and hemagglutination. Bioorganic & medicinal chemistry. 2013; 21(15):4706-13.
191. Schwarz S, Sauter D, Wang K, Zhang R, Sun B, Karioti A, Bilia AR, Efferth T, Schwarz W. Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta medica. 2014; 80(02-03):177.
192. Cho JK, Curtis-Long MJ, Lee KH, Kim DW, Ryu HW, Yuk HJ, Park KH. Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of Paulownia tomentosa. Bioorganic & medicinal chemistry. 2013; 21(11):3051-7.
193. Roh C. A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide. International journal of nanomedicine. 2012; 7:2173.
194. Chiow KH, Phoon MC, Putti T, Tan BK, Chow VT. Evaluation of antiviral activities of Houttuynia cordata Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. Asian Pacific journal of tropical medicine. 2016 Jan 1; 9(1):1-7.
195. Kim S, Hwang BY, Su BN, Chai H, Mi Q, Kinghorn AD, Wild R, Swanson SM. Silvestrol, a potential anticancer rocaglate derivative from Aglaia foveolata, induces apoptosis in LNCaP cells through the mitochondrial/apoptosome pathway without activation of executioner caspase-3 or -7. Anticancer research. 2007; 27(4B):2175-83.
196. Son KH, Oh HM, Choi SK, Han DC, Kwon BM. Anti-tumor abietane diterpenes from the cones of Sequoia

- sempervirens. *Bioorganic & medicinal chemistry letters*. 2005; 15(8):2019-21.
197. Yang CW, Lee YZ, Kang IJ, Barnard DL, Jan JT, Lin D, Huang CW, Yeh TK, Chao YS, Lee SJ. Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. *Antiviral research*. 2010; 88(2):160-8.
 198. Wen CC, Kuo YH, Jan JT, Liang PH, Wang SY, Liu HG, Lee CK, Chang ST, Kuo CJ, Lee SS, Hou CC. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *Journal of medicinal chemistry*. 2007; 50(17):4087-95.
 199. Yang CW, Chang HY, Lee YZ, Hsu HY, Lee SJ. The cardenolide ouabain suppresses coronaviral replication via augmenting a Na⁺/K⁺-ATPase-dependent PI3K_PDK1 axis signaling. *Toxicology and applied pharmacology*. 2018; 356:90-7.
 200. Koehn FE, Sarath GP, Neil DN, Cross SS. Halitunal, an unusual diterpene aldehyde from the marine alga *Halimeda tuna*. *Tetrahedron letters*. 1991; 32(2):169-72.
 201. Macintyre G, Curry B, Wong F, Anderson R. Hygromycin B therapy of murine coronaviral hepatitis. *Antimicrobial agents and chemotherapy*. 1991; 35(10):2125-7.
 202. Cheng PW, Ng LT, Chiang LC, Lin CC. Antiviral effects of saikosaponins on human coronavirus 229E in vitro. *Clinical and Experimental Pharmacology and Physiology*. 2006; 33(7):612-6.
 203. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive care medicine*. 2013; 39(2):165-228.
 204. Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, Xu H. Positive RT-PCR test results in patients recovered from COVID-19. *Jama*. 2020 Apr 21; 323(15):1502-3.
 205. Dave JB. Novel Coronavirus Pandemic- Stark Realities & New Lessons for Science & Humanity. *Pharma Times*. 2020; 52 (4): 9-14.

Peer-review

External peer-review was done through double-blind method.

Article History

Received: 03 November 2020

Reviewed & Revised: 04/November/2020 to 16/December/2020

Accepted: 17 December 2020

Prepared: 21 December 2020

Published: January 2021

Publication License



© The Author(s) 2021. Open Access. This article is licensed under a Creative Commons Attribution License 4.0 (CC BY 4.0).

General Note



We recommended authors to print article as color digital version in recycled paper. Discovery Scientific Society will not provide any prints for subscription.